# INVASIVE STREP A: WHAT DO WE NEED TO KNOW?



# HEARING

BEFORE THE

## HUMAN RESOURCES AND INTERGOVERNMENTAL RELATIONS SUBCOMMITTEE

OF THE

## COMMITTEE ON GOVERNMENT OPERATIONS HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRD CONGRESS

SECOND SESSION

JULY 28, 1994

Printed for the use of the Committee on Government Operations



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# CONTENTS

# INVASIVE STREP A: WHAT DO WE NEED TO KNOW?

THURSDAY, JULY 28, 1994

HOUSE OF REPRESENTATIVES,
HUMAN RESOURCES AND
INTERGOVERNMENTAL RELATIONS SUBCOMMITTEE
OF THE COMMITTEE ON GOVERNMENT OPERATIONS,
*Washington, DC.*

The subcommittee met, pursuant to notice, at 10 a.m., in room 2154, Rayburn House Office Building, Hon. Edolphus Towns (chairman of the subcommittee) presiding.

Present: Representatives Edolphus Towns, Donald M. Payne, Steven Schiff, and Rob Portman.

Also present: J. Allen Hill, professional staff member; Martine M. DiCroce, clerk; and Martha Morgan, minority professional staff, Committee on Government Operations.

## OPENING STATEMENT OF CHAIRMAN TOWNS

Mr. TOWNS. The Subcommittee on Human Resources and Intergovernmental Relations will come to order.

Today the Subcommittee on Human Resources and Intergovernmental Relations looks at the public health concerns from invasive group A streptococcus. Millions of people get some form of strep infection each year in the United States. Far fewer get invasive infections but several thousand die each year.

Our purposes in the hearing are twofold: first, to take expert testimony in a public meeting so that the public can be adequately and accurately informed about strep A and what they should do to protect themselves from its consequences; and second, to consider our current state of understanding about strep A, our facilities for monitoring and studying it, and determine whether those are adequate to meet the threat that we are facing.

Most of us have read or seen reports of the flesh-eating bug. Necrotizing fasciitis is a gruesome condition, just as strep toxic shock is a scary one. As a grandparent, of course, I know how often children have strep throat. If there is a comforting word in all of this, it is that children get 80 percent of the mild cases of strep, but only 10 percent of the invasive or serious cases. What remains unknown is why some people—of any age—will get the mild form when exposed to strep, while others get the invasive form.

Before the 1950's, the many threatening consequences of invasive strep made it a source of active concern to public health officials everywhere. Since then, our monitoring of strep has dropped dramatically.

Today, it competes with many other infectious diseases for reporting and monitoring resources. Is that a mistake we should correct? Are our resources adequately arrayed to detect and respond to emerging infectious disease threats?

At this time, I would like to yield to the ranking minority member of the subcommittee, Congressman Schiff.

Mr. SCHIFF. Thank you, Mr. Chairman.

First I want to thank you very much for holding this hearing. I think it is on a very important subject. As you indicated, group A streptococcus has been around for a long time, and has been the cause for a number of illness, most of which there has ordinarily been a speedy recovery from. Most recently I have seen in the press, reports of necrotizing fasciitis which I at least had not seen before in the media, and it at least suggests to me if not a new disease, an outbreak of this disease.

And what struck me was my recollections of HIV-positive and AIDS, when that came into the news in the early 1980's, and I believe that those cases were reported in the press very much like necrotizing fasciitis is being reported now, as an unusual but extremely rare disease.

We have since learned that AIDS is not obviously a rare disease and it is an epidemic in portions of the United States and in portions of the entire world. And what I believe we should accomplish at this hearing is to determine, is there a similar threat from any of the diseases that might be caused by group A streptococcus, whether it is this particular disease that deals with the loss of skin tissue and organ tissue or any other resulting disease.

And I have to say, Mr. Chairman, nothing would please me better if the experts who are about to testify so state that this is something that can be contained and is being contained. But I think the threat of this disease is significant enough that we don't want it to be another HIV, we don't want to find out 10 years from now that it really was something that we didn't do anything about.

I look forward to the testimony.

Mr. TOWNS. Thank you very much, Congressman Schiff.

At this time, I yield to Congressman Payne for any opening statement he might have, or remarks.

Mr. PAYNE. Thank you very much, Mr. Chairman.

Let me commend you this morning for calling this hearing and for the leadership that you have taken in many of the issues relating to health that we have been dealing with. I also wanted to extend my regards to the panel of witnesses who have agreed to provide us with their testimony.

I think the media attention that has been devoted to the outbreak of the so-called flesh-eating bacteria has probably contributed to a general hysteria about the possibilities of a widespread epidemic.

I would hope that during the course of this hearing that we would clarify the threat to the public health and correct some of the misinformation-feeding frenzy that has been created regarding the situation.

This particular infection of necrotizing fasciitis actually develops in about 5 to 10 percent of cases of strep, which is about 1,000 to

1,500 cases overall. And this invasive infection develops in about 10 to 20 percent of pediatric cases of strep infection.

Additionally, there is some evidence that Native Americans may be more susceptible to invasive infections, especially in the Southwest regions, where they are observed to suffer a higher incidence of several bacterial diseases.

One area study found African-Americans are twice as likely as whites to contract invasive strep A. The most vulnerable population are diabetics, immune-compromised persons, intravenous drug users, and alcoholics. These segments of the population often receive little or no medical attention until their condition becomes critical because their access to medical care is restricted.

Modern medicine has come a long way in virtually eliminating diseases that once proved fatal. We saw this with polio, scarlet fever, and rheumatic fever. However, in the last decade, we have dropped our guard on diseases like tuberculosis, committing fewer and fewer resources each year to protecting the public health. And now, as a result, there is a resurgence of a more hostile strain of tuberculosis, which is more difficult to treat and deadly.

The greater issue at hand is that now that the health threat associated with strep has been abated, the mechanisms necessary to ensure that there is not a resurgence of a strep epidemic are not in place.

To my understanding, it remains to be seen if the CDC is sufficiently equipped to detect whether or not there is a recurring trend in the incidence of invasive strep in our population. Many times we move in the wrong direction of cutting in areas where we need to have increases, and increases in areas where we don't need them in our budgets, as we saw in the 1980's with defense and other areas of growth, and we saw a reduction in the services needed, especially for vulnerable populations.

Mr. Chairman, let me thank you again for calling this hearing today. I think there are some very important issues that need to be addressed, and I look forward to hearing the testimony of our witnesses.

Mr. TOWNS. Thank you very much.

Let me thank you and Congressman Schiff for your opening statements. And I think that you are right, we need to collect information.

At this time I would like to call on Dr. Claire Broome to come to the witness table, Deputy Director of the Centers for Disease Control. And Dr. Dennis Stevens, chief of the infectious disease section of the Veterans Affairs Medical Center in Boise, ID.

May I remind both of you—first of all, let me welcome you to the hearing and say that your entire statement will be included in the record. If you would just summarize within 5 minutes and allow us to raise some questions with you, I think we will be able to accomplish a lot more that way.

So, Dr. Broome, why don't you begin.

## STATEMENT OF CLAIRE V. BROOME, M.D., DEPUTY DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION

Dr. BROOME. Thank you, Mr. Chairman. I am Dr. Claire Broome, Deputy Director of the Centers for Disease Control and Prevention.

I am pleased to respond to the subcommittee's invitation to provide testimony on severe infections caused by group A streptococci.

Group A streptococci are bacteria which cause a wide variety of infections ranging from common, often clinically mild illnesses such as strep throat, scarlet fever, and impetigo, to rare and often severe infections such as pneumonia, necrotizing fasciitis, and streptococcal toxic shock syndrome.

The initial site of infection is usually the nose or throat or the skin. Invasive infection develops when the organism gets through the usual body defenses leading to infection in the blood, lungs, or other normally sterile sites. Bacteria are transmitted person to person through respiratory secretions.

Severe and fatal infections caused by group A streptococci have been recognized since the 1800's. Necrotizing fasciitis, which was first reported in 1918, is characterized by infection and destruction, or necrosis, of soft tissue.

Necrotizing fasciitis usually begins with infection at the site of a break in the skin. About 15 percent of necrotizing fasciitis cases result in death.

Streptococcal toxic shock syndrome was first reported in 1987. Streptococcal toxic shock syndrome is defined by the isolation of group A streptococcus from a normally sterile site and the early development of shock with involvement of multiple organ systems such as kidneys, lungs, and liver. The case fatality rate of persons with this syndrome exceeds 60 percent.

To define the incidence of severe infections and identify risk factors, CDC has collaborated with State and local health departments to conduct surveillance for all group A streptococcal infections where the bacteria were isolated from the patients' blood. These investigations showed an annual rate of bloodstream infection between 3.5 and 6.8 cases per 100,000 persons, approximately 10,000 to 15,000 cases in the United States each year.

Among these cases, 10 to 15 percent met the definition for streptococcal toxic shock syndrome, and 3 to 7 percent had necrotizing fasciitis. Rates of disease are higher in Native Americans and African Americans than in whites. The age group at highest risk is the elderly.

What is CDC doing to monitor the occurrence of group A streptococcal infection? We monitor these infections in several different ways. We do special epidemiologic and laboratory surveillance to get precise estimates of the rate, and that is the basis for the rates I have just quoted to you.

We also use the network of State and local health departments who are contacted by local physicians when clusters of cases occur. We also track bacteria sent to the CDC laboratory. CDC is one of only two institutions in the United States that can classify group A streptococcal isolates by M type, which is a way of subtyping the bacterium.

The recent changes in the occurrence of severe infection and streptococcal toxic shock syndrome correspond to a dramatic increase in the proportion of strains of two particular subtypes, types M–1 and M–3. Reports from other countries of increases in invasive group A streptococcal infections and M–1 infections suggest an in-

creasing proportion of virulent M–1 group A streptococci that began in the 1980's and continues today.

CDC has taken several approaches to the prevention and control of invasive group A streptococcal infections. These include educating physicians and other health care providers through CDC's reports and other scientific publications, presentations at scientific meetings and interviews with the media. We try to inform physicians so that they consider the diagnosis of severe group A streptococci when they see a patient and treat aggressively when appropriate.

Invasive group A streptococcal infection, streptococcal TSS and necrotizing fasciitis present examples of emerging public health challenges. CDC's strategic plan for addressing these challenges is outlined in the document, "Addressing Emerging Public Health Threats: A Prevention Strategy for the United States," which I would like to submit for the record.

Mr. TOWNS. Without objection, so ordered.

Dr. BROOME. Thank you, Mr. Chairman.

[The information may be found in the subcommittee files.]

Dr. BROOME. Investments in laboratory research and training, and prevention and control programs will ensure we are better prepared to respond to these threats and lessen their impact through a prevention-oriented public health policy.

Thank you for the opportunity to testify before the subcommittee. I will be happy to answer your questions.

[The prepared statement of Dr. Broome follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

Statement of

Claire V. Broome, M.D.

Deputy Director

Centers for Disease Control and Prevention

Public Health Service

Department of Health and Human Services

before the

Subcommittee on Human Resources

and Intergovernmental Relations

Committee on Government Operations

U.S. House of Representatives

July 28, 1994

I am Dr. Claire V. Broome, Deputy Director of the Centers for Disease Control and Prevention (CDC). I am pleased to respond to the Subcommittee's invitation to provide testimony on severe infections caused by group A streptococci bacteria.

Group A streptococci are bacteria which cause a wide variety of infections ranging from common, often clinically mild illnesses such as "strep throat," scarlet fever, and impetigo (a common skin infection), to rare and often severe or fatal infections such as pneumonia, necrotizing fasciitis, and streptococcal toxic shock syndrome (STSS). Group A streptococcal infections also may lead to autoimmune illnesses including rheumatic fever, which is a leading cause of chronic valvular heart disease, and acute glomerulonephritis, a disease which may result in kidney failure. In my testimony, I will respond to the issues raised in your letter of invitation concerning the clinical, epidemiologic, and laboratory characteristics of severe group A streptococcal infections, focusing on the emergence of streptococcal toxic shock syndrome and necrotizing fasciitis; describe CDC's efforts to monitor these conditions and the trends in their occurrence; and comment on the nature of severe group A streptococcal disease as a public health threat.

In addition, I will discuss CDC's recently released strategic plan for addressing emerging infectious disease threats in the United States. This plan was released in April 1994 and addresses the priorities, set forth by the National Academy of Science's Institute of Medicine (IOM), to safeguard the nation from the threat of emerging infectious diseases. I would like to submit a copy of the CDC plan, "Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States," for your consideration for the record.

Group A streptococci cause disease only in humans and have no reservoir other than man. The initial site of infection is generally the upper respiratory tract (nose and throat) or skin. Infection may result in clinical illness or the bacteria may be carried asymptomatically in the throat or on the skin. Invasive infection develops when the organism enters the body through the skin or from a mucosal site, leading to infection in the blood (bacteremia), lungs (pneumonia), or other normally sterile sites. Community studies have shown that group A streptococci may be carried in the throats of up to 30 percent of healthy school children. The bacteria are transmitted person-to-person through respiratory secretions. Group A streptococci do not survive well in the environment so that infection rarely is spread by contact with environmental surfaces.

Severe and fatal infections caused by group A streptococci have been recognized since the late-1800s when it was identified as the cause of puerperal sepsis, an infection that resulted in the death of thousands of women each year after childbirth.

Necrotizing fasciitis was first reported in 1918. Following a recent cluster of cases with necrotizing fasciitis in Gloucestershire, United Kingdom, interest has been heightened in this complication of group A streptococcal infection. This infection is characterized by infection and destruction (necrosis) of soft tissue including fascia or connective tissue, muscle, and fat. Necrotizing fasciitis usually begins with infection at the site of a break in the skin and may progress rapidly. Initial signs are those of a skin infection including pain, redness, and swelling, in association with fever. As the disease progresses signs of systemic illness, such as shock, may occur along with extensive tissue destruction requiring surgical removal of diseased tissue or amputation of an extremity. Reported case-fatality rates from necrotizing fasciitis have ranged from 10 to over 50 percent. In a CDC investigation of invasive group A streptococcal infections in San Francisco during the period 1991 until May 1994, 14 percent of necrotizing fasciitis cases ended in death.

A previously unrecognized illness, the group A streptococcal toxic-shock syndrome (STSS), was first reported in 1987, although cases had most likely occurred before that time. Two years later, a report describing 20 patients with STSS from the Rocky Mountain states suggested that this syndrome was becoming more common. A Working Group of academic and public health experts, convened by CDC, published a consensus case definition of the syndrome (The Working Group on Severe Streptococcal Infections. Defining the Group A Streptococcal Toxic Shock Syndrome. JAMA 1993;269;390-391), which is characterized by isolation of group A *Streptococcus* from a normally sterile site and the early evolution of clinical signs of low blood pressure (shock), and involvement of multiple organ systems including impairment of the kidneys, liver and lungs, disorders of blood clotting, generalized skin rash, and soft tissue necrosis. Over half of STSS cases begin with an infected skin lesion and one-quarter occur in conjunction with pneumonia. The case-fatality rate of persons with this syndrome exceeded 60 percent in the San Francisco investigation, as well as in a recent investigation in Canada.

To define the incidence of severe infections and identify risk factors, CDC has collaborated with State and local health departments to conduct surveillance for all group A streptococcal disease. All cases where the bacteria were isolated from the patient's blood (bacteremic infection) were identified in defined populations in parts of California, Arizona, New Mexico, Colorado, Ohio, and Maryland. The results of these investigations indicated an annual rate of bacteremic infection between 3.5 and 6.8 cases per 100,000 population, which would translate to an annual occurrence of approximately 10,000 to 15,000 cases each year in the United States. In all surveillance areas, the rate of disease in African-Americans was higher than

in whites; the highest incidence of disease was identified in American Indians, who, in a Pima County, Arizona, study had a 15-fold higher risk of disease than other racial or ethnic groups. The age group at highest risk was the elderly and, although children have high rates of mild group A streptococcal infections, they were at low risk for developing bacteremia or STSS. Bacteremic disease was most likely to occur during the winter and spring months.

Among the cases of invasive group A streptococcal infection detected by surveillance, 10-15 percent met the case definition for STSS, and 3-7 percent had necrotizing fasciitis. Risk factors for infection included underlying diseases such as diabetes mellitus, alcohol and intravenous drug abuse, and HIV infection. Breaks in the skin are the most common site from which invasive infection develops. These invasive infections may range from seemingly insignificant injuries (such as the scratch of a thorn while gardening) to major trauma or surgical incisions.

Because there is no ongoing national surveillance for invasive group A streptococcal infections, it is difficult to determine trends in the occurrence of disease. However, several types of evidence suggest an increase in the rate and the severity of invasive group A streptococcal infections over the past decade. Hospital-based case series in several areas have indicated increases in the number of invasive cases in the later half of the 1980s. Surveillance for all invasive cases in the San Francisco Bay area between 1989-94 showed peaks in disease incidence in 1989 and 1994, with the smallest number of cases occurring in 1991. In Pima County, although surveillance between 1987-90 showed no change in the overall rate of disease, there was a significant increase in the occurrence of STSS, from 0 percent before 1988 to 8 percent in 1989-90. This study indicated no change in the occurrence of necrotizing fasciitis.

Laboratory-based investigations of group A streptococci have made important contributions to our understanding of the pathogenesis of severe group A streptococcal infections. Laboratory-based surveillance data also suggest an increase in the rate and severity of disease. Although there are approximately 80 different serotypes of group A streptococci, two specific serotypes, M-1 and M-3, have been associated with the recent increase of severe invasive infections. Since 1972, approximately 6,000 group A streptococcal isolates have been analyzed at CDC. During this period, the serotype distribution of invasive isolates has changed dramatically with the proportion of M-1 strains increasing from 3 percent in 1972 to almost 40 percent in 1989. Between 1989 and 1993, M-1 decreased to approximately 15 percent of invasive isolates, but this year has again increased to more than 30 percent. Similar, although not as dramatic, changes have occurred in the proportion of M-3

strains which increased from less than 3 percent prior to 1980 to 18 percent in 1994. Analysis of the serotype and clinical data demonstrates that infection with an M-1 or M-3 strain was significantly more likely to result in STSS, and in death, than infection with other group A streptococcal types.

CDC investigations to determine possible virulence factors for severe group A streptococcal infections demonstrated a significant association between STSS and infection with strains that produce a specific toxin, pyrogenic exotoxin A. Necrotizing fasciitis was associated with the activity of proteases, which are enzymes that can break down proteins. Pyrogenic exotoxin A production was significantly more likely to be found in M-1 and M-3 strains than in other group A streptococci. Protease activity also was significantly more common among M-1 strains. Laboratory tests for detection of pyrogenic exotoxin A production in isolates collected between the 1950s and the late-1980s demonstrated that few strains produced this toxin during that period of time. Recent increases in the proportion of isolates making this toxin correspond to changes in the strain distribution and the occurrence of STSS.

There is no evidence that mutations have occurred which would increase the virulence of individual group A streptococcal strains. Genetic material (DNA) coding for pyrogenic exotoxins can be transferred between group A streptococci on plasmids, which are small pieces of genetic material that may be inserted in some bacterial cells. Whether virus (or phage) mediated transfer of plasmids between strains plays any role in the changes in disease spectrum remains hypothetical.

Some group A streptococci have developed resistance to the antibiotic erythromycin, a recommended therapy for noninvasive infections in penicillin-allergic patients. Clindamycin and other effective antibiotics can be used to treat penicillin-allergic patients who have invasive infection. No group A streptococci strains have yet been documented to be penicillin-resistant, and penicillin remains the treatment of choice for group A streptococcal infections.

Although data from other countries are limited, reports from Great Britain, Scandinavia, and Australia showed increases in the incidence of invasive group A streptococcal infections and in the proportion of M-1 infections occurring during the late-1980s. In addition, CDC has received isolates from patients with STSS in Latin America and Asia all of which have been type M-1. These data suggest a pandemic of virulent M-1 group A streptococci that began in the 1980s and is continuing today.

Invasive group A streptococcal infections, STSS, and necrotizing fasciitis present evolving public health challenges and represent a problem of emerging infectious diseases. The

estimated 10,000 to 15,000 annual cases and 1,500 to 3,000 annual deaths from these infections place a substantial burden on the health care system. Moreover, the illness can be catastrophic and may occur in previously healthy individuals after seemingly minor trauma. Additionally, clusters of invasive infection have occurred in the military, nursing homes, hospitals, and families. Historical data on the occurrence of severe group A streptococcal infections in the past 150 years have suggested that, superimposed on an overall decline in incidence, occasional changes in strain distribution and virulence periodically occur. In the second half of the 19th century, significant increases in the case-fatality rate for scarlet fever occurred at approximate 10-year intervals. During the Second World War, thousands of cases of rheumatic fever and other streptococcal infections occurred in military trainees; a large proportion of these cases were caused by serotypes that are uncommon today.

Although invasive illness may occur in otherwise healthy persons, one's own immune system and other host factors are important in determining the likelihood of invasive disease. For example, the clinical effect of the same M-1 strain infection may vary significantly within a family. Investigations of households where a case of STSS occurred showed that a strain that causes STSS in one family member may result only in a sore throat or asymptomatic throat carriage of the bacteria in others. The importance of host factors also is suggested by the infrequent occurrence of invasive infection and STSS in children, although this age group accounts for approximately 80 percent of mild group A streptococcal infections.

The changes in occurrence of severe group A streptococcal infections in the past decade emphasize the importance of CDC's working with State health departments to monitor the incidence, clinical, and laboratory characteristics of invasive infections. Currently, there is little routine data collection and reporting of invasive group A streptococcal infections. Surveillance of infectious diseases in the United States is heavily dependent upon voluntary collaborations between CDC and State and local health departments, which in turn depend on physician-initiated reporting of a limited number of specific, recognized infectious diseases. Reporting is generally incomplete. State health departments determine which diseases must be reported to them by physicians and diagnostic laboratories within their borders and, through the Council of State and Territorial Epidemiologists (CSTE), which diseases the States will report to CDC. In many States, the demands of current reporting requirements have exceeded the available resources, making additional disease reporting difficult.

Despite these constraints, CDC has responded to the changes in severe group A streptococcal infections by collaborating with State and local health departments to develop sentinel population-based surveillance systems. In addition, changes in

serotype distribution nationwide have been monitored by laboratory testing of isolates sent to CDC. CDC also has provided technical assistance to State health departments in investigating outbreaks of severe group A streptococcal infections.

It is important that appropriate surveillance of invasive group A streptococcal infections and other emerging pathogens be conducted at State and national levels. The capacity to perform serotyping for group A streptococcal isolates in the United States is only available at CDC and the University of Minnesota. This capacity must be maintained, as changes in M-type distribution may be used to track changes in clinical disease.

Enhancing infectious disease surveillance, and strengthening the public health infrastructure at the local, State, and Federal levels to provide needed laboratory support and training are major priorities included in the CDC plan for prevention of emerging infectious disease threats. The changes in occurrence of severe group A streptococcal infections during the past decade demonstrate how infectious diseases may increasingly threaten public health and contribute significantly to the escalating costs of health care.

Results from a recent survey by the Council of State and Territorial Epidemiologists illustrate the inadequacy of existing infectious surveillance by documenting the limited number of professional positions dedicated to infectious disease surveillance in most states. Funding for communicable disease surveillance is largely limited to diseases for which public health crises have already developed (TB, HIV/AIDS, sexually transmitted diseases, and selected vaccine-preventable diseases). No Federal resources are provided to State and local health departments to support the national notifiable disease surveillance system. The ability of state public health laboratories to support the surveillance, diagnosis, and control of infectious diseases has diminished.

Technological advances and changes in the health care system will provide opportunities for new approaches to surveillance. Managed care systems have resulted in large databases which may provide broad-based, high-quality surveillance data. Recent efforts to improve electronic data collection from state public health laboratories with the introduction of the Public Health Laboratory Information System (PHLIS) may facilitate future surveillance efforts.

In addition to comprehensive and innovative surveillance systems, effective preparation for emerging infectious diseases requires sound foundations in professional expertise, laboratory support, and research capability. These foundations support the infrastructure needed to address the ongoing, but often changing, threats from emerging infections. To meet the broad challenges

of new and reemerging infectious diseases, CDC must maintain modern molecular biologic expertise in infectious disease threats, and transfer this technology to State public health laboratories.

Implementation of the CDC plan for prevention of emerging infections will require long-term collaborations and partnerships with public health agencies, universities, private industry, and communities. Improved State and local public health surveillance and laboratory capacity are critical components of the plan, including training for public health laboratory personnel in modern techniques for detection of emerging diseases. Highest priority activities would include providing assistance to state and local health departments to strengthen epidemiologic and laboratory-based surveillance, enhancing diagnostic laboratory capacity in health departments and at CDC, and establishing sentinel surveillance networks to monitor emerging diseases such as invasive group A streptococcal infections, antibiotic-resistant diseases, foodborne diseases and community-acquired pneumonia.

CDC has taken several approaches to the prevention and control of invasive group A streptococcal infections. These approaches have included educating physicians and other health care providers through information provided in CDC's Morbidity and Mortality Weekly Report and other medical and scientific publications, presentations at medical and scientific meetings, and interviews with the media. CDC investigation of disease clusters have led to recommendations for controlling the spread of disease in nursing homes and for preventive therapy or chemoprophylaxis in certain settings. Identification of an increased risk for severe infection in specific patient groups will permit the development of focused interventions to decrease risk in those populations. Finally, through collaborations with clinicians and laboratory researchers, CDC is working to better define optimal treatment for infection and to identify factors associated with organism virulence which, in the long term, may provide opportunities for prevention through the development of effective vaccines.

Investments in surveillance, laboratory research and training, epidemiologic investigations, and integration of results into prevention and control programs will ensure that we are better prepared to respond to emerging infectious disease threats and to lessen their impact. It is crucial that emerging infectious diseases be addressed and that the basic principles of prevention-oriented public health policy form an integral component of our nation's efforts to safeguard health in our communities.

Thank you for the opportunity to testify before the subcommittee. I will be happy to answer your questions.



85-648 O - 94 - 2

Mr. TOWNS. Thank you very much, Dr. Broome.
Dr. Stevens, please proceed.

**STATEMENT OF DENNIS L. STEVENS, M.D., Ph.D, CHIEF, INFECTIOUS DISEASE SECTION, VETERANS AFFAIRS MEDICAL CENTER, BOISE, ID**

Dr. STEVENS. My name is Dennis L. Stevens. I am chief of infectious disease at the Veterans Affairs Medical Center, Boise, ID. I am here to talk about the clinical aspects of group A streptococcal infection as well as to provide a research perspective on the host parasite interactions.

As Dr. Broome has said, we and others have certainly described invasive group A streptococcal infections in this country as well as other parts of the world. And I am not going to go into all the details of the necrotizing fasciitis and toxic strep, but instead would like to just make five points that I think I have come to grips with in the last 5 or 6 years in working with group A strep.

First is that I think that the prevalence of this infection has not increased dramatically in the last 5 or 6 years, but has remained relatively constant, and in fairly low numbers, as Dr. Broome has suggested. We continue to see these invasive forms of group A streptococcal infection and, as we speak, people in this Nation are acquiring this disease and dying.

The second point is to point out that group A strep is not just a cause of toxic strep syndrome and the necrotizing fasciitis but causes many other very common maladies of children as well as adults. And those have been reiterated by Dr. Broome and certainly are incorporated in my testimony.

The third point is that there are many different kinds of group A streptococci, and each type may cause one, two or several different kinds of group A streptococcal infections, and I would have to admit that the scientific community does not understand why different strains can cause different kinds of infection, but it is an area of hot research investigation at the present time.

The fourth point is that the virulence of group A strep can vary over time, and the literature, the older literature, in particular is replete with examples of this. And I would just like to point out that perhaps there is no better example than in the case of scarlet fever, and I would just like to read you a comment.

For example, in New York City and Chicago, in 1890, when one compares the mortality of scarlet fever from 1890 compared to 1920, in both cities in 1890 between 25 and 30 percent of all children with scarlet fever died. Twenty-five percent, 25 out of every hundred died of scarlet fever. In contrast, by 1920, the mortality rate was less than 5 percent, and currently it is less than 0.5 percent.

One can conclude from these data that either host factors changed or the organism's virulence changed over time. I must remind the subcommittee that antibiotics were not available until the 1930's or 1940's; so it had nothing to do with things physicians or public health officials did. It had a lot to do with the virulence of the organism and its striking changes.

So that means that we have to keep an eye on the organism and we need to monitor the severity of not just the severe forms of group A streptococcal infection but all forms, in my opinion.

The fifth point I would like to make is that humans are really the only reservoir of group A strep in nature, and this means that many public health measures such as providing potable water, inspecting meat, properly cooking pork, practicing safe sex, et cetera, things that work very well in other kinds of infectious diseases we deal with in the United States today, do not work. And so that means that we need to be cognizant of diagnosing and treating these kinds of infections very quickly.

So in summary, I think there is a clear and ever-present danger of serious group A streptococcal infections in every geographical area of the world. If history repeats itself, as it is wont to do, we can expect waxing and waning of severe group A streptococcal infections to occur.

I think it is difficult for us to predict whether the current severe group A streptococcal infections we have seen will decrease, stay the same, or increase. But I think we need to be prepared to meet that challenge.

So I think in summary I would say that I think, number one, we need to constantly monitor all types of group A streptococcal infections and not just zero in on the severe forms.

We need to improve reporting and active surveillance of these diseases.

We need to determine the precise mechanisms of pathogenesis and host response through basic science research.

We need to monitor antibiotic resistance in this organism, because development of penicillin resistance in group A streptococci would be a true disaster.

We need to develop new and novel therapies, including potential vaccines as well as better ways to treat shock and tissue destruction in these severe infections, because modern treatments still result in a very high mortality and morbidity in such cases.

And I would be glad to answer any questions relative to my testimony.

Thank you, sir.

[The prepared statement of Dr. Stevens follows:]

DEPARTMENT OF VETERANS AFFAIRS
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July 28, 1994

In Reply Refer To
531/Bldg. 6

Edolphus "Ed" Towns, Chairman,
Subcommittee on Human Resources
and Intergovernmental Relations
Congress of the United States
House of Representatives
2157 Rayburn House Office Building
Washington D.C. 20515-6143

Statement of Testimony by Dennis L. Stevens, MD, PhD, Chief Infectious Disease Section, Veterans Affairs Medical Center, Boise, Idaho and Professor of Medicine, University of Washington School of Medicine, Seattle, WA.

Congressmen Towns, Members of the Subcommittee on Human Resources and Intergovernmental Relations, colleagues and guests:

It is an honor and a privilege to testify before this group regarding invasive Group A streptococcal infections.

Since the mid-1980's reports of aggressive Group A streptococcal infections associated with shock, multiorgan failure and a high mortality rate began to appear. Individuals most commonly affected appeared to be otherwise healthy individuals and not those who would be considered immunocompromized. In 50% of cases we could not determine the portal of entry. Patients usually developed a prodrome of fever, chills, confusion and in 70-80% of cases increasing pain at the site of minor, non-penetrating trauma that subsequently became infected. Patients with such infection rapidly developed low blood pressure, renal failure, liver failure and shock. (Please find an enclosed paper previously published in the New England Journal of Medicine which details the salient features of this disease). In spite of antibiotics, intensive care unit treatment, intravenous fluids and surgical procedures which frequently involved amputation of one or more extremities, 30-70% of patients died. It is the later feature of these infections that has caught the fancy of the world press, who refer to this organisms as the "Flesh Eating Bacteria". Luckily, the American press and television networks have been much more reasonable than the British tabloids in their reporting. Over the course of the last 5-10 years, we and others have worked diligently to determine what is unique about the strains of streptococci that cause such infections, and to investigate the means that this bacteria and its toxins interact with the human host to cause such fulminant destruction.

I would like to make 5 points regarding streptococcal infections which will briefly

convey my perspectives based upon my work with patients, colleagues and in the research laboratory.

The first point is to put in proper perspective the significance of the recent worldwide emergence of severe life threatening streptococcal infections. There is little question that in the United States and throughout the world a more severe form of Group A streptococcal infections has occurred. It must be emphasized that the numbers of these cases has remained low and that the recent flurry in the press has been more because of the dramatic nature of these infections than because of a real threat of spread of such infection among the populace at large. Studies done by public health laboratories in this country and abroad have shown that the risk of an epidemic of this type of infection is quite low. However, citizens from many countries have developed fulminant streptococcal infections and 30-70% have died in spite of the best that modern medicine has to offer. Cases continue to be recognized, though an increase in the frequency of these cases has not materialized.

The second point is to recognize that Group A streptococcus causes many different types of infections. Pharyngitis (sore throat) is the most common, and is the leading reason why children are taken to pediatricians in the United States. Streptococcal pharyngitis causes significant absenteeism in elementary schools and afflicts children in day care centers as well. Untreated streptococcal pharyngitis can lead to rheumatic fever, scarlet fever and a kidney disease called post-streptococcal glomerulonephritis. Rheumatic fever and nephritis occur not during the acute phase of infection, but usually 2-3 weeks after the streptococcal infection and are clearly due to the host's response to infection rather than the infection per se. A variety of skin and soft tissue infections also are caused by Group A streptococcus such as erysipelas, impetigo lymphangitis and cellulitis. Ear infections, mastoid infections, sinus infections, meningitis, pneumonia, bacteremia, muscle infection (myositis) and deep connective tissue infection (necrotizing fasciitis) are other types of infections caused by Group A streptococcus. Recently, acquired attention deficits and learning disabilities have been reported in some children following Group A streptococcal infections as well.

The third point is that there are many different types of Group A streptococci, and each type may cause one, two, or all of the types of infections described above.

The fourth point is that the virulence of Group A streptococcus can vary over time; this is reflected in human terms by changes in the severity of infection. There is no better example of this than the statistics on the mortality of scarlet fever in New York City and Chicago in 1890 compared to 1920. In both cities in 1890, between 25-30% of all children with scarlet fever died. In contrast by 1920 the mortality was less than 5%. It must be remembered that antibiotics were not available until the 1930-1940 era. One can conclude from these data that striking changes in the virulence of the organism occurred during this period of time. It is of interest that the severity of scarlet fever has remained low during the rest of the 20th century. There

are many other examples of striking changes in the virulence of Group A streptococcal infections throughout history that time does not permit me to describe.

The fifth point that I would like to make is that humans are the major, if not exclusive, reservoir of Group A streptococcus in nature. This means that many public health measures such as providing potable water, inspecting meat, properly cooking pork, practicing safe sex etc. will do little or nothing to prevent spread of infection among the public. This also means that the human host and the pathogen have each established a complicated list of factors which interact with each other. It is these interactions that determine whether or not an infection will develop. In my opinion, understanding of these interactions is of paramount importance if we are to determine why certain people develop rheumatic fever for example, and why some do not. Only basic science research will establish why in a given family, one child has died of streptococcal toxic shock syndrome, another sibling has developed scarlet fever, the mother has developed streptococcal pharyngitis, and the father was an asymptomatic carrier of this organism.

In summary, there is a clear and ever-present danger of serious Group A streptococcal infection in every geographical area of the world. If history repeats itself, as it is want to do, we can expect increased frequency and severity of a wide variety of streptococcal infections.

It is imperative that we:

- constantly monitor and report all types of Group A streptococcal infections,
- improve reporting and active surveillance of these diseases,
- determine the precise mechanisms of streptococcal pathogenesis and host response through basic science research,
- monitor antibiotic resistance,
- develop new and novel treatments, including potential vaccines, for all types of streptococcal infections.

Those of us who are involved in streptococcal research and patient care must educate physicians through the medical and scientific literature, continuing medical education courses, conferences and lectureships.

Finally, in this age of health care reform in which individuals are encouraged to

participate in health care decisions involving themselves and family members, we must provide accurate and understandable information to the general population regarding these diseases.

Thank you for the opportunity to address this committee and for your kind attention.

Sincerely,

DENNIS L. STEVENS, Ph.D., M.D.
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Mr. TOWNS. I thank you very much, Dr. Stevens, and I also thank you, too, Dr. Broome.

At this time I would like to yield 5 minutes to Congressman Schiff for any questions that he might have.

Mr. SCHIFF. Thank you, Mr. Chairman, for yielding to me.

I want to thank both Dr. Stevens and Dr. Broome for their testimony. And I want to say that I suggested this hearing for the following reason. It is clear, as has been testified to, that streptococcus infection is not new. It has been among humankind for many, many years in one form or another.

It is also clear that in the news media recently, somewhat emphasized by tabloid journalism, emphasis on the so-called flesh-eating disease or the necrotizing fasciitis, as I believe it is formally called, that there is a new media attention on streptococcus infections.

And the key question I would like to ask both of you in turn—I will start with you, Dr. Broome—is this question. Either through an increase in quantity of infections from streptococcus or through an increased number of severe forms of infection, do we face a more severe threat from streptococcus infections today than we did, say, five or 10 years ago?

Dr. BROOME. I do agree with Dr. Stevens that the actual rate of bloodstream infections seems to be relatively constant. But I do think there has been an increasing proportion caused by strains that have been linked to necrotizing fasciitis and the streptococcal toxic shock syndrome. So this is one of the reasons we think it is so important to monitor the bacteria.

If you were just counting cases, you might miss this shift. You need to look at the clinical syndromes and you need to look at the bacteria to identify the fact that there seems to have been a change.

Mr. SCHIFF. Now, let me state this back to make sure I have it. I believe you have testified that the number of cases overall reported involving group A streptococcus infections has remained relatively stable, but the number of cases involving the more severe diseases that can result from that has increased within that number?

Dr. BROOME. That is correct. I would like to clarify that these rates are actually not based on reporting in the usual sense of somebody notifying a health department. That is a relatively unreliable way of determining rates of disease, because it can be affected by things like media attention, for example.

When we try to get a rate for this disease, we go out and define areas and review the microbiology laboratory records to find how many isolates of group A streptococci have been made from cultures of the blood. So for the special studies that we have done, we have a fairly good ability to define the rate of disease.

Mr. SCHIFF. Dr. Stevens, are you in agreement that the overall number is relatively stable but the incidence of a more severe form of this streptococcus-caused disease is apparent?

Dr. STEVENS. Well, I think that is a difficult question, and I agree that I don't think the reporting has really been adequate. Although the CDC has done some active surveillance in a five-State area and whatnot, still, reporting of this disease is largely, as was

alluded to, based upon the individual responsiveness of physicians and whatnot. It is not mandatory. If a physician is busy, he may or may not report to the State health department.

So I think nationwide the numbers aren't as reliable as they could be. They certainly aren't as good as we have with AIDS and things of that nature.

Because I am recognized as someone who is interested in this disease and has been for many years, I hear about cases from frantic physicians calling wanting to know how to manage these cases. And so I have a bias, obviously, because I hear about a lot of these cases. And I wouldn't want to give you the impression that my experience is anywhere reflective of what is actually going on in the country. But I get phone calls nearly every day from all over the United States about these severe infections.

I think I would also like to say that although it was stated that this can be a disease associated with compromised patients, in fact this is a disease that, while it may infect compromised patients, it more commonly affects patients who are perfectly well. In fact, it is our bias that it takes a good immune system to really develop the toxic shock syndrome. And it is really the organism and its virulence factors trick the host into overreacting and causing shock and multiorgan failure. So it may be less common in compromised patients.

Mr. SCHIFF. I am getting somewhat of an impression, though, that our information and our data on the question I asked about what is happening out there as a public health matter is uncertain to say the least. Is that right, Dr. Stevens?

Dr. STEVENS. I agree. And I think the CDC has done a great job with the resources that it has in doing the study in the five-State area. But I think we need to be more cognizant of the total picture of group A strep, pharyngitis, scarlet fever, rheumatic fever, and all the other complications.

This is a common disease that causes a tremendous amount of economic and physical problems among Americans. And I think we need to be more diligent in dealing with it.

Mr. SCHIFF. My time is up. I thank both witnesses, and I yield back, Mr. Chairman.

Mr. TOWNS. Thank you very much, Congressman Schiff.

At this time I yield to Congressman Payne for any questions that he might have.

Mr. PAYNE. Thank you very much.

In your testimonies, you both stated that the number of people infected with necrotizing fasciitis is low and remains low. However, we have seen with the increase in AIDS, because of people whose immune systems are compromised, we have seen a corresponding increase in tuberculosis.

Do you feel, although just listening to your last answer, do you feel that there could possibly be an increase in that population that have a compromised immune system?

Dr. STEVENS. Well, I will take a shot at that. The group A strep is probably one of the most difficult pathogens that we deal with, because it can cause such fulminate infections, even in normal people. Certainly elderly individuals, malnutritioned individuals, and

people who have compromised immune systems who are in the hospital are also susceptible.

I don't want to give you the impression that group A strep infections never occur in that population. They certainly do. It is just that the more fulminate form, the rapid onset of shock and that sort of disease, tends to be more common among those of us such as in this room that are intact immunologically. But I think it certainly is a problem in all individuals irrespective of their immune status.

Dr. BROOME. Representative Payne, we do have some data from San Francisco, which is one of the areas where we did the special studies, and in that population the overall rate of group A streptococcal bacterinia was 6.5 per 100,000. So it was within the rate that we have seen in other areas.

A number of those patients did have AIDS. So they are one of the groups of immunocompromised who are at increased risk for invasive group A streptococcal disease. But AIDS is not a major contributor to the overall rate.

Mr. PAYNE. Let me ask you this. If there should be an outbreak, do you think that we are prepared adequately to handle it?

I don't want to put you on the spot. Maybe we ought to ask Dr. Stevens. But either one of you may want to respond.

Dr. BROOME. Well, as Dr. Stevens has indicated, this is a difficult disease to deal with. You cannot—it is not like a food-borne outbreak where you can remove the contaminated source of food. The major approaches are to be sure that physicians are very alert to the diagnosis, and treat promptly and aggressively when appropriate.

If the outbreak occurs in a very defined setting, such as a nursing home or a daycare center, it is possible to treat with prophylactic antibiotics—if you have got a very clearly defined situation.

The kind of disease that we are talking about is really spread throughout the entire population so that those kinds of approaches with prophylactic antibiotics would not be feasible.

I very much support Dr. Stevens' statement that we do need more basic science research and efforts for a vaccine development, which would be one approach for ultimate prevention of group A streptococcal disease.

Mr. PAYNE. Just finally, there were examples of this disease in England or in other parts of Europe. Has CDC been in any kind of formal relations with your European counterparts, and have you been able to discover anything?

Dr. BROOME. Yes, we have been in contact with the Public Health Laboratory Service in the United Kingdom and we were able to ascertain quite promptly that they were investigating a small cluster of six cases in Gloucester. But they also knew from their laboratory based surveillance that the overall rate of group A streptococcal invasive disease was relatively constant, so that they could show they were not experiencing a major epidemic.

And even the cluster of cases in Gloucester were not all of the same M subtype, so they did not appear to be related to each other. It may have just been one of those very unusual clusters.

Mr. PAYNE. Thank you very much.

Mr. TOWNS. Thank you very much, Congressman Payne.

Let me begin by asking: Prior to the media getting involved, this thing seemed to have been treated in a very casual kind of way, like "don't say anything and don't do anything," basically. Is my opinion and my assessment of that accurate?

Dr. STEVENS. I don't think that is true. One of the first articles that I think really portrayed this, although there were several case reports of toxic strep syndrome prior to 1985 and 1986, was an article that we were involved in writing in the New England Journal of Medicine which actually got a lot of attention from the medical community, the scientific community and the press throughout the United States and the world.

About a year later, the late Jim Henson developed a fulminate group A streptococcal infection; in his case it was pneumonia. Once again there was a tremendous increase in the press coverage, and there were articles in newspapers, Newsweek, and CBS nightly news and so on.

So I think back in 1989 and 1990, there was a lot of interest in the medical scientific community as well as the American press. I don't know why the British press was totally unaware of this, because, as you all know, a few months ago when they had the cases in England, they acted like this has never been described. And that wasn't the case at all. This has been well recognized by the scientists and medical doctors and CDC, et cetera, here in the United States, 4 or 5 years previously.

Mr. TOWNS. Let me ask another question to make certain I have a clear understanding here. There are only two labs in the country that can do the blood work, is that what you are saying?

Dr. BROOME. Well, group A streptococcus can be isolated by any bacteriology laboratory. There is a special subtype——

Mr. TOWNS. There has been 75 of them, right, at least in terms—from my understanding, 75 different bacterias?

Dr. BROOME. The two laboratories I was referring to are able to do the specialized subtyping to identify—to track the change in strain characteristics over time. So that is what I was referring to in my testimony.

Any bacteriology laboratory in a hospital would be able to isolate and identify group A streptococcus without difficulty.

Mr. TOWNS. Your lab would be one of the labs you were talking about as the two in the country? Yours is one?

Dr. BROOME. Yes.

Mr. TOWNS. Let me get some background information. What are the warning signs of necrotizing fasciitis and toxic shock? What are the warning signs one would look for?

Dr. STEVENS. In the reports you have before you, I could just summarize those, since they are written in medical terms. Most patients that develop the streptococcal toxic shock syndrome have fever and they have chills. Those that develop necrotizing fasciitis usually have increasing and excruciating pain, usually in an extremity.

Sometimes there is no other symptom than the pain. There may not be any physical evidence of things going on beneath the skin. As hours go by, the skin can become red, it can become hot and tender, and then bullae or blisters appear over the skin, and at that point in time there is usually extensive destruction of tissue,

not only in the skin but the subcutaneous fat, the fascia and deep muscle.

These people by that time also have shock, organ failure, and mortality rates are exceedingly high. So early on, fever and chills and unexplained pain are the best signs and symptoms that we have to go on.

Mr. TOWNS. How quickly should a person seek treatment?

Dr. STEVENS. I am sorry, sir.

Mr. TOWNS. How quickly does a person need to get treatment?

Dr. STEVENS. Well, I think by the time they develop pain, probably the infection has been incubating for several days. But by the time they have pain, things can progress to shock and organ failure within 24 hours. So the earlier antibiotic treatment can be begun, the better the results.

So all I can tell you is that patients that have fever, chills, and unexplained pain should seek medical care immediately. If caught early enough, antibiotics are very effective.

Mr. TOWNS. Dr. Stevens, you had an observation that does bear on the need for aggressive treatment of mild cases. Do we ever see mild strep infections become invasive ones? If so, could you elaborate on that?

Dr. STEVENS. Well, if you had asked me that question a year ago I would have said probably not. But in the last year, I am certainly aware of patients that have had run of the mill group A strep pharyngitis who subsequently have developed streptococcal toxic shock syndrome.

And in many of the articles that I have written and other people as well, strep pharyngitis or sore throat has been a very unusual manifestation of these more fulminate infections. So it can. And so for that reason I think that we really have to be very aggressive about diagnosing strep throat and treating it appropriately.

Now, in Scotland, for example, they have pretty much done away with doing throat cultures, perhaps because of health care costs, et cetera, and I really think that would be a disaster for us to try to do in this country. I think we need to know what is going on. We need to identify things that are readily treatable. And then we need to treat them aggressively.

I think your point is well taken. Minor problems can develop into more severe ones if they aren't dealt with appropriately.

Mr. TOWNS. Let me ask a very , very basic question. Do we know what role diet plays in strep infections? Does diet play any part in this?

Dr. BROOME. As I mentioned, we have been able to show that there are increased rates of disease in some populations. We do not have good information on more detailed risk factors. And those are some of the studies that we would like to do, for example, nutritional status, or other possible factors which might affect people's susceptibility to severe group A streptococcal disease.

Mr. TOWNS. My time has expired. Did any of the other members have any other questions?

Mr. SCHIFF. Mr. Portman.

Mr. TOWNS. I am sorry, we have been joined by Congressman Portman.

Let me thank both of you for your testimony. This is an area that I really feel that we need to pursue in a very aggressive fashion, as I think Congressman Schiff pointed out, that we might look down the road some years from now—I think Congressman Payne said as a result of not doing something now in a very aggressive kind of way—we find we have really missed the point here. So I am hoping we can create the kind of atmosphere and climate to go and look and see whether or not diet or some of these other factors affect strep infections, and see what we can do to deal with them.

In order to do that, sometimes you might have to ask for additional resources. That is something you might need to begin to think about, because I don't think strep infection is going to go away. I think we have seen that it is not going to go away. And in fact the only way we can hope that we will be able to get it under control is by getting the research and getting information to be able to treat people and treat them early. I think that is essential.

So I thank both of you for your testimony, Dr. Stevens and Dr. Broome.

Dr. STEVENS. Mr. Chairman, could I ask that the articles I submitted be included into the record?

Mr. TOWNS. Without objection, your entire statement will be included in the record and also the articles you submitted.

[The information follows:]

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## SEVERE GROUP A STREPTOCOCCAL INFECTIONS ASSOCIATED WITH A TOXIC SHOCK-LIKE SYNDROME AND SCARLET FEVER TOXIN A

DENNIS L. STEVENS, M.D., PH.D., MARTHA H. TANNER, M.D., JAY WINSHIP, M.D., RAYMOND SWARTS, M.D., KRISTEN M. RIES, M.D., PATRICK M. SCHLIEVERT, PH.D., AND EDWARD KAPLAN, M.D.

# SEVERE GROUP A STREPTOCOCCAL INFECTIONS ASSOCIATED WITH A TOXIC SHOCK–LIKE SYNDROME AND SCARLET FEVER TOXIN A

DENNIS L. STEVENS, M.D., PH.D., MARTHA H. TANNER, M.D., JAY WINSHIP, M.D., RAYMOND SWARTS, M.D., KRISTEN M. RIES, M.D., PATRICK M. SCHLIEVERT, PH.D., AND EDWARD KAPLAN, M.D.

**Abstract** There is concern that group A streptococci, which have caused less serious infections in developed countries in recent decades, may be acquiring greater virulence. We describe 20 patients from the Rocky Mountain region who had group A streptococcal infections from 1986 to 1988 that were remarkable for the severity of local tissue destruction and life-threatening systemic toxicity.

Among the 20 patients (median age, 36), necrotizing fasciitis with or without myositis was the most common soft-tissue infection (55 percent). Nineteen patients (95 percent) had shock, 16 (80 percent) had renal impairment, and 11 (55 percent) had acute respiratory distress syndrome. The mortality rate was 30 percent. All patients but 1 had positive tissue cultures for *Streptococcus pyogenes;* 12 had positive blood cultures. Most of the patients had no underlying disease; 2 used intravenous drugs. Strains of group A beta-hemolytic streptococci isolated from 10 patients were not of a single M or T type; however, 8 of the 10 strains produced pyrogenic exotoxin A (scarlet fever toxin A, a classic erythrogenic toxin), which has rarely been observed in recent years.

From our study of this cluster of severe streptococcal infections with a toxic shock–like syndrome, we conclude that in our region, more virulent group A streptococci have reappeared that produce the pyrogenic toxin A associated with scarlet fever. (N Engl J Med 1989; 321:1-7.)

DRAMATIC declines in the prevalence of both rheumatic fever and serious infection caused by group A streptococci have been observed throughout the 20th century in much of the Western world.[1-4] The decline has been thought by some[2,3] to be related in part to improved socioeconomic conditions, timely treatment of streptococcal pharyngitis with antibiotics, and secondary prophylaxis for rheumatic fever.[2,3] Stollerman[5] has argued that this decline is a function of the changing potential of the organism to cause rheumatic fever and other major diseases. The recent outbreaks of acute rheumatic fever reported in middle-class children in Utah[6,7] as well as in Pennsylvania,[8] California (Navy recruits),[9] Ohio, and Missouri (Army recruits),[10] may reflect renewed virulence of streptococci. Similarly, the recent outbreaks of streptococcal pharyngitis in the United States,[9-11] the newly recognized streptococcal toxic shock–like syndrome,[12-14] and the severe streptococcal infections reported recently from Great Britain[15] could all be related to changes in the expression of other virulence factors of *Streptococcus pyogenes.*

During the past two years we have observed an apparent increase in the virulence of *S. pyogenes,* as manifested by a variety of unusually severe soft-tissue infections associated with marked systemic toxicity. These infections have occurred primarily among normal hosts in the Rocky Mountain area of the United States. This report describes 20 patients with group A streptococcal soft-tissue infection associated with high morbidity and mortality. Our study of these patients with a streptococcal toxic shock–like syndrome[12-14] documents the reappearance of scarlatina toxin among clinical isolates of streptococci from our region.

From the Infectious Disease Service, Veterans Administration Medical Center, Boise, Idaho (D L S ), the Department of Medicine, University of Washington, Seattle (D L S ), Eastern Idaho Regional Medical Center, Idaho Falls (M H T ), Missoula Community Hospital, Missoula, Mont (J W ), Washoe Medical Center, Reno, Nev (R S ), University of Utah and Holy Cross Hospital, Salt Lake City (K M R ), and the Department of Microbiology (P M S ), the Department of Pediatrics (E K ), and the World Health Organization Collaborating Center for Reference and Research on Streptococci (E K ), University of Minnesota, Minneapolis. Address reprint requests to Dr Stevens at 500 W Fort St , Boise, ID 83702

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## METHODS

### Case Reporting

Severe cases of streptococcal soft-tissue infection were first noted in January 1984 in Boise, Idaho. The identification and collection of subsequent cases in Montana (four cases), Idaho (seven), Utah (eight), and Nevada (one) were the result of awareness of the clinical features of such infections, maintained through communications among a group of infectious-disease specialists in the Rocky Mountain region (the Rocky Mountain Pus Club). Two cases occurred in

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1984, one in 1985, five in 1986, five in 1987, and seven in 1988. Because such cases of severe streptococcal infection are not reportable to state or local health departments, no estimates of the prevalence of this infection are available for the years preceding 1984. However, because of the dramatic presentation of this illness, it seems unlikely that many earlier cases were overlooked, especially in our region of the United States. Our criteria for identifying cases were the isolation of *S. pyogenes* in cultures of blood, body fluid, or tissue and evidence of severe soft-tissue, pharyngeal, or blood-borne infection.

### Serotyping of Streptococci

Clinical isolates were obtained from cultures of blood, tissue of the fascia, muscle, uterus, vagina, or pharynx, sputum, peritoneal fluid, or joint fluid. Organisms suspected to be streptococci were identified according to standard bacteriologic criteria. Group A streptococci were initially identified by their degree of sensitivity to bacitracin and then were grouped in the clinical microbiology laboratory with the use of Streptex kits (Wellcome Diagnostics, Burroughs Wellcome, Research Triangle Park, N.C.). Specimens of group A streptococci were forwarded to the World Health Organization Collaborating Center for Reference and Research on Streptococci (University of Minnesota), where serologic grouping and typing for M protein, T-agglutination pattern, and opacity factor were carried out according to standard techniques.[14-19]

### Pyrogenic Exotoxin

Isolates of group A streptococci were evaluated for their production of pyrogenic exotoxin, with use of an Ouchterlony immunodiffusion test.[20] Organisms were grown overnight in a dialyzable beef-heart medium,[21] without shaking, until the stationary phase at 37°C was achieved. Subsequently, toxins were concentrated by ethanol precipitation and restoration with distilled water to 1 percent of the original culture volume.[21]

## Results

### Factors Associated with Group A Streptococcal Soft-Tissue Infection

Sixteen of 20 patients in this series were 50 years of age or younger, and 12 were younger than 40 (Table 1). The mean ages of the 11 men and 9 women were similar (42 and 39 years). Thirteen of the patients were completely well before the onset of their illness.

Two of the seven patients with possible predisposing factors (Table 2) consumed liberal amounts of alcohol (five or six beers per day), although neither had clinical signs of alcoholism, and both were gainfully employed. One patient had adult-onset diabetes mellitus and required insulin during the infection. One patient was obese, and another had moderate neurologic dysfunction after undergoing craniotomy for an acoustic neuroma years before. Two patients had used illicit drugs intravenously; one used them habitually, and the other had experimented with them just before the onset of the streptococcal infection.

The suspected portal of entry was the skin in nine patients and the mucous membrane in four (Table 2). Of the latter group, two patients had vaginal infections that occurred eight days and five weeks post partum, respectively; the other two had positive throat cultures. Streptococcal infection developed in two patients within 48 hours of surgical procedures (suction lipectomy in one and hysterectomy in the other), and in two others after minor trauma (elbow abrasion during an accident in one, and a small hematoma on the hand in the other). The portal of entry was unknown in seven patients.

### Symptoms Associated with Streptococcal Infection

Pain was the most common initial symptom in 17 patients (85 percent) and was frequently abrupt in onset and severe. Four patients required narcotic analgesics to control the pain, and two presented with pain and no other physical findings. The pain usually involved an extremity but was intraabdominal in two patients. Before its onset, four patients had an influenza-like syndrome characterized by fever, chills, myalgia, and diarrhea. Altogether, 5 patients had vomiting, 6 had diarrhea, 13 had chills, and 5 had myalgia.

### Physical Findings

Fourteen patients (70 percent) presented with an oral temperature above 37°C (Table 3). Two patients had hypothermia and shock at the time of admission. Eleven patients were confused at admission; one patient's mental status deteriorated rapidly to coma, and two others were combative. The confusion was particularly severe in one patient, who had advanced renal failure and shock by the time she was taken to the hospital and died within 96 hours. Most patients (80 percent) had tachycardia, and over half (55 percent) had a systolic blood pressure below 110 mm Hg. In eight of the nine patients with normal blood pressure (systolic pressure, 110 mm Hg or more), marked hypotension and shock developed within four hours of admission. Localized swelling and erythema were present in 13 patients (Table 3). One additional patient presented with bullous skin lesions; two others had soft-tissue swelling alone. No patients had a rash typical of scarlatina, although two had petechial rash, two had maculopapular rashes, and four had desquamation 7 to 14 days after admission. Of the four patients who presented without dermal manifestations of infection, one had shock and was ultimately found to have endophthalmitis, one had fulminant myositis eight hours after presentation, one had perihepatitis after a hysterectomy, and one presented with spontaneous peritonitis, myocarditis, and sepsis.

### Hematologic Tests

The mean white-cell count was only 11,765 cells per cubic millimeter. However, the differential cell count was striking in that 43 percent of cells were immature (band forms, metamyelocytes, or myelocytes). Platelet counts were estimated by microscopy as normal in 6 of the 20 patients. The mean platelet count exceeded 216,000 per cubic millimeter in the 13 patients in whom quantitative platelet counts were performed; by 72 hours it had dropped to 129,000. The prothrombin time, determined in 10 patients, was prolonged by more than three seconds in 6, of whom 4 had bacteremia and 2 did not. Initially, the mean hematocrit value was normal (43 percent) for the altitude of the area

Table 1. Clinical Characteristics and Courses of 20 Patients with Group A Streptococcal Infection.

| Patient No. (Yr of Diagnosis) | Age/Sex | Clinical Presentation | Clinical Course | | | | | Outcome |
|---|---|---|---|---|---|---|---|---|
| | | | Shock | ARDS* | Renal Impairment | Surgery | Bacteremia | |
| 1 (1984) | 66/M | Myalgia, pharyngitis | + | + | + | Debridement | + | Died |
| 2 (1984) | 41/M | Joint sepsis, necrotizing fasciitis | + | + | | Amputation | − | Lived |
| 3 (1985) | 29/F | Cellulitis (right leg, post partum) | + | + | + | | + | Died |
| 4 (1986) | 67/F | Cellulitis, osteomyelitis | + | + | + | Debridement | + | Lived |
| 5 (1986) | 63/M | Shock, pharyngitis, endophthalmitis | + | + | + | | + | Lived |
| 6 (1986) | 33/M | Suppurative thrombophlebitis | + | | + | Debridement | + | Lived |
| 7 (1986) | 30/M | Cellulitis | + | | + | Debridement | − | Lived |
| 8 (1986) | 42/M | Necrotizing fasciitis (elbow) | + | + | + (dialysis) | Debridement | + | Died |
| 9 (1987) | 33/M | Necrotizing fasciitis | + | | + | Debridement | − | Lived |
| 10 (1987) | 34/F | Cellulitis, probable myositis | + | + | + (dialysis) | | − | Died |
| 11 (1987) | 35/F | Septic shock, necrotizing fasciitis | + | + | + | Debridement | − | Lived |
| 12 (1987) | 61/M | Cellulitis | + | + | + | Debridement | + | Died |
| 13 (1987) | 42/F | Cellulitis (forearm) | + | | + | Debridement | − | Lived |
| 14 (1988) | 25/F | Infection at site of suction lipectomy | + | + | + | Debridement | − | Lived |
| 15 (1988) | 48/F | Shock, peritonitis (posthysterectomy) | + | | + | Laparotomy | − | Lived |
| 16 (1988) | 34/F | Myometritis (post partum) | + | + | + | Hysterectomy | + | Lived |
| 17 (1988) | 31/M | Infection (thumb), necrotizing fasciitis | − | − | − | Amputation | + | Lived |
| 18 (1988) | 29/M | Peritonitis, myocardiopathy | + | | + | | + | Lived |
| 19 (1988) | 37/F | Axillary pain, sore throat | + | | | Debridement | + | Lived |
| 20 (1988) | 36/M | Septic shock | + | | | | + | Died |

*Acute respiratory distress syndrome

(700 to 1460 m [2300 to 4800 ft] above sea level); however, by 48 to 72 hours it had dropped to 29 percent.

### Blood Chemistry Values

Initially, serum creatinine concentrations were elevated in 17 of 19 patients tested (mean, 222 μmol per liter [2.5 mg per deciliter]), and they increased to a mean of 302 μmol per liter (3.4 mg per deciliter) by 48 to 72 hours. The concentrations returned to normal several weeks to months later in all but two patients; both patients had progressive azotemia and required dialysis. Serum calcium levels, measured in 15 patients, were low on admission (mean, 2.03 mmol per liter [8.1 mg per deciliter]) and continued to drop over the next three days (mean, 1.65 mmol per liter [6.6 mg per deciliter]). The mean serum albumin level (n = 15) also was low on admission (33 g per liter [3.3 g per deciliter]) and dropped further by the third hospital day (23 g per liter [2.3 g per deciliter]). Thus, the degree of hypocalcemia was greater than expected solely on the basis of the degree of hypoalbuminemia. In support of this observation, concentrations of ionized calcium were also low in the two patients studied (0.25 and 0.4 mmol per liter [1.0 and 1.6 mg per deciliter]). Serum creatine kinase, measured serially, increased to a mean of 113,685 IU in 8 of 10 patients by 48 to 72 hours. Of these eight patients, one had myocarditis (creatine kinase, 1359 IU; MB fraction, 12 percent), one had myositis and necrotizing fasciitis, and five had necrotizing fasciitis. Three of these five also had probable myositis. In two of these last three

Table 2. Factors Associated with Group A Streptococcal Soft-Tissue Infection.

| Factor | No. of Patients (%) |
|---|---|
| No. of patients | 20 |
| Underlying disease | |
| Diabetes mellitus, adult onset | 1 (5) |
| Obesity | 1 (5) |
| Alcoholism | 2 (10) |
| Cerebellar ataxia | 1 (5) |
| Intravenous drug abuse | 2 (10) |
| No known predisposing factor | 13 (65) |
| Probable portal of entry | |
| Skin | |
| Leg ulcer, osteomyelitis | 1 (5) |
| Local trauma | 2 (10) |
| Surgical procedure | 2 (10) |
| Intravenous drug abuse | 2 (10) |
| Infected hair follicle | 1 (5) |
| Chronic leg ulcer | 1 (5) |
| Mucous membrane | |
| Vaginal area, post partum | 2 (10) |
| Pharynx | 2 (10) |
| Unknown | 7 (35) |

patients, intractable shock, acute respiratory distress syndrome, and renal failure ensued; in neither patient was a surgical procedure or an autopsy performed.

### Urinalysis

The test for hemoglobin (Hemastix) was positive in 12 of 17 patients. All 12 patients had elevated serum creatinine concentrations at the time of admission. Five of the 17 patients also had microscopic hematuria, but invariably with fewer than five red cells per high-power field. Thus, the presence of hematuria among patients with serious group A streptococcal infection correlated well with the presence of renal impairment.

### Bacteriologic Cultures

Group A streptococci were grown from blood, body fluid, or tissue from all 20 patients. Nineteen had positive cultures of tissue obtained by surgical biopsy, fasciotomy, or percutaneous aspiration. One patient (Patient 20), who died in the emergency room, had positive blood cultures only. In addition, group A streptococci were grown from pharyngeal specimens from two patients and from vaginal specimens from two others. Overall, 12 patients had positive blood cultures (Table 4).

### Clinical Course

Twelve of the 20 patients (60 percent) had bacteremia, and 6 (30 percent) died. Of these, five died within 96 hours of admission, and three died within 36 hours. The morbidity among patients in this series was high (Table 4); 13 patients underwent major surgical procedures, which included fasciotomy (9 patients), debridement other than fasciotomy (2), amputation (2), exploratory laparotomy (1), intraocular aspiration (1), and hysterectomy (1). Desquamation of the skin developed in four patients between the 7th and 10th days after diagnosis.

Table 3. Physical Findings at the Time of Admission.

| Finding | No. of Patients (%) |
|---|---|
| No. of patients | 20 |
| Temperature (°C) | |
| ≤37 | 6 (30) |
| >38 | 14 (70) |
| Confusion | 11 (55) |
| Heart rate (beats/min) | |
| 80–99 | 4 (20) |
| 100–140 | 11 (55) |
| >140 | 5 (25) |
| Systolic blood pressure (mm Hg) | |
| ≥110* | 9 (45) |
| 90–109 | 4 (20) |
| 70–89 | 4 (20) |
| ≤69 | 3 (15) |
| Skin | |
| Swelling only | 2 (10) |
| Swelling, erythema | 13 (65) |
| Bullae | 1 (5) |
| No swelling | 4 (20) |

*In eight of nine patients with high systolic blood pressure (>110 mm Hg) on admission, hypotension developed within four hours

Table 4. Complications of Group A Streptococcal Soft-Tissue Infection.

| Complication | No. of Patients (%) |
|---|---|
| No. of patients | 20 |
| Shock | 19 (95) |
| Acute respiratory distress syndrome | 11* (55) |
| Renal impairment | 16 (80) |
| Irreversible | 2 (10) |
| Reversible | 14 (70) |
| Amputation | 2 (10) |
| Desquamation of the skin | 4 (20) |
| Fasciotomy | 9† (45) |
| Sepsis | 12 (60) |
| Death | 6 (30) |

*Diffuse pulmonary edema and hypoxia developed in one patient, both complications were resolved with diuresis and supplemental oxygen

†Amputation of a limb was ultimately required in two patients who underwent fasciotomies

The site of infection was confirmed by surgical intervention in the majority of cases (Table 1). Necrotizing fasciitis was the most common presentation (8 patients [40 percent]). Cellulitis alone was found in two patients; in one, the serum creatine kinase level was normal, and surgical exploration confirmed that muscle was not infected. Some of the cases of necrotizing fasciitis presented clinically as cellulitis (three cases), but a poor response to antibiotics or an elevation of the creatine kinase level prompted surgical intervention, on which substantial muscle involvement was found. Two patients presented with peritonitis, which occurred after a hysterectomy in one patient (Patient 15) and appeared spontaneously in the other, a mountain climber (Patient 18), who presented with severe pain in the left lower quadrant and one day later had myocarditis and group A streptococcal bacteremia. Other patients presented with osteomyelitis, endophthalmitis, joint sepsis, myometritis, or suppurative thrombophlebitis.

Shock was apparent at the time of admission or within hours thereafter in 19 patients (Table 4). In two patients, the systolic blood pressure became normal four to eight hours after they had received intensive monitoring, dopamine infusion, albumin, and electrolyte solutions containing salts. In others, shock persisted. Acute respiratory distress syndrome occurred in 11 of the 20 patients and was generally diagnosed after the onset of hypotension. Of the 11 patients with the syndrome, 10 required intubation, supplemental oxygen, and mechanical ventilation.

Renal impairment was apparent at admission in 17 patients and persisted or progressed in all 17 for 48 to 72 hours. Progressive azotemia requiring dialysis developed in only two patients. In all the patients who survived, serum creatinine values returned to normal within four to six weeks (data not shown).

### Characteristics of Clinical Isolates of Group A Streptococci

All strains isolated from the patients were bacitracin-sensitive, Lancefield group A streptococci (Table

Table 5. Characteristics of Clinical Isolates of Group A Streptococci.

| Patient No (Yr of Diagnosis) | Lancefield Group* | Type | | Pyrogenic Exotoxin | | |
|---|---|---|---|---|---|---|
| | | T | M† | A | B | C |
| 1 (1984) | A | 3 | 3 | + | – | – |
| 11 (1987) | A | 1 | 1 | + | + | – |
| 12 (1987) | A | 3 | 3 | + | – | – |
| 13 (1987) | A | 11 | NT | + | + | + |
| 15 (1988) | A | 1 | 1 | + | + | – |
| 16 (1988) | A | 3 | 3 | + | – | – |
| 18 (1988) | A | 28 | 28 | + | – | – |
| 18 (1988) | A | 28 | 28 | – | – | – |
| 19 (1988)† | A | 1 | 1 | – | + | – |
| 20 (1988) | A | 11 | NT | + | + | – |

*All strains were bacitracin-sensitive and produced streptolysin O

†Mucoid colony NT denotes not typable

5). Only one strain of the 10 studied further had mucoid colony morphology; that strain was an M-1. M-3–T-3 and M-1–T-1 were the most prevalent strains. The prevalence of pyrogenic exotoxin A (scarlet fever toxin) was striking among the strains isolated in this study (8 of 10 strains). Only one M-1 strain and one M-28–T-28 strain did not produce this toxin. Two different strains of M-28–T-28 were isolated from the blood of one patient (Patient 18); one of these strains was opacity-factor–positive and pyrogenic exotoxin A–negative, and the other strain was opacity-factor–negative and pyrogenic exotoxin A–positive. This was confirmed by repeated testing.

## Discussion

This study and others[4-15] suggest that the frequency of severe group A streptococcal infections may have increased. Of the 20 patients we have described, 19 had shock, 12 had bacteremia, and 6 died of group A streptococcal infections. Host factors do not appear to explain these outcomes, since 80 percent of our patients were less than 50 years of age, most did not have underlying disease, none were immunocompromised, and most did not have obvious portals of entry. This is in striking contrast to other series of patients with group A streptococcal sepsis, in which age, diabetes, alcoholism, and drug abuse were found to be important risk factors.[22-27]

Most patients in our series presented with a soft-tissue infection, such as cellulitis or necrotizing fasciitis. In addition, several patients had deeper infection, including osteomyelitis, myometritis, peritonitis, suppurative phlebitis, and endophthalmitis. Most presented with hypotension, renal dysfunction, hypoalbuminemia, hypocalcemia, and respiratory failure. These clinical features and the multisystem failure are similar to those described by Todd and Fishaut[28] in patients with the staphylococcal toxic shock syndrome and by Cone et al.,[12] Bartter et al.,[13] and Hřibalová[14] in patients with the streptococcal toxic shock–like syndrome. A major difference between our patients and those with staphylococcal toxic shock syndrome[28] is that ours had extensive soft-tissue infection and bacteremia. In contrast, that syndrome is usually not associated with bacteremia, and the site of infection may be difficult to identify.[28] In the present series, surgical intervention was of major importance in establishing a diagnosis and removing devitalized tissue.

Some characteristics of group A streptococci that recently have been associated with increased virulence include mucoid colony morphology (hyaluronic acid capsule) and M-1, M-3, and M-18 serotypes.[6,10,15,29,30] Specifically, mucoid strains of the M-18 serotype have recently been associated with epidemics of pharyngitis[10] and acute rheumatic fever.[6] In contrast, no association has been identified between T or M type and either suppurative soft-tissue infection or sepsis caused by group A streptococci.[31] The prevalence of M and T types among the strains isolated in the present study was also noteworthy, since an epidemic of acute rheumatic fever was occurring simultaneously in roughly the same area.[6]

Interestingly, 6 of our 10 isolates were M type either 1 or 3 (Table 5). These findings are in contrast to reports from New Zealand, where no specific M or T type was associated with severe suppurative infections in children.[31] All three of the M-3 strains were isolated from patients in Idaho. Only one strain in the current series had mucoid colony morphology, and this strain was type M-1. This is in marked contrast to an outbreak of pharyngitis, in which most mucoid strains were of M-18 (74 percent) or M-3 (20 percent) type.[10] The prevalence of pyrogenic exotoxin A among the clinical isolates from our patients (8 of the 10 isolates examined) was striking. This observation is particularly important since none of 80 strains of group A streptococci isolated from clinical sources in the United States between 1976 and 1986 produced pyrogenic exotoxin A.[2] Similarly, strains of group A streptococci isolated during outbreaks of mild scarlet fever in England from 1980 to 1985 produced type B and type C pyrogenic exotoxin, but none produced type A.[32] Earlier in this century in the United States, exotoxin A was highly prevalent among clinical isolates, particularly those associated with scarlet fever.[12,33] In addition, of four isolated reference strains from patients who had severe scarlet fever in England before 1940, all produced pyrogenic exotoxin A.[32] In a recent editorial, Stollerman[5] discussed this issue and concluded that changes in the prevalence of type A pyrogenic toxin among strains may help to explain the historical relation of streptococci to scarlet fever and toxic shock syndrome.

Factors that support a role for streptococcal toxin in our patients include the marked destruction of tissue and the multiple organ failure. Indeed, the constellation of renal failure, shock, hypocalcemia, and thrombocytopenia is similar to that seen in staphylococcal toxic shock syndrome, which is clearly a toxin-mediated illness. That pyrogenic exotoxin A could mediate these clinical derangements is strongly suggested by its known biologic properties, shared with toxic shock syndrome toxin-1, which include the following[29-32]: pyrogenicity, enhancement of susceptibility to endotoxin shock, enhancement of delayed hypersensitivity to induced skin rashes, cytotoxicity (including cardiac

damage), mitogenicity (nonspecific) for T lymphocytes, immunosuppression (of B-lymphocyte function), alteration of host antibody response, and mitogenic activity in humans and in lymphocytes from rabbits.[33-36]

In this regard, the observation (Lee PK, Schlievert PM: unpublished observations) that pyrogenic exotoxin type A was lethal to rabbits when administered by osmotic pumps over seven days, whereas identical amounts of type C toxin were not lethal, is important. One additional mechanism of shock induced by toxic shock syndrome toxin-1 and probably by pyrogenic exotoxin A is direct myocardial depression.[37] The absence of a rash in some patients with scarlet fever in this study may reflect a lack of previous sensitization to pyrogenic exotoxins, which is thought to be necessary for the production of a rash in scarlet fever.[38] Numerous patients with the toxic shock syndrome have also been reported to be without a demonstrable rash.[39]

The role of other toxins, such as streptolysin O (thiol-activated cytolysin), in the pathogenesis of infection in our patients is conjectural, yet such toxins are lethal,[40,41] produce shock,[40,41] and also directly depress myocardial contractility.[42] Perhaps the higher prevalence of shock, acute respiratory distress syndrome, renal failure, and death observed in our patients could be due in part to the additive effects of pyrogenic exotoxin A and streptolysin O (Table 5).

Other explanations for shock and renal failure must also be considered, particularly among patients with bacteremia. Bacteremia could have resulted in complement activation, disseminated intravascular coagulopathy, and shock mediated by bradykinin or other biologically active endogenous mediators. Yet, the prevalence of shock, renal failure, and mortality was not greater among the patients with bacteremia (92 percent, 75 percent, and 33 percent, respectively) than among those without it (100 percent, 86 percent, and 25 percent, respectively). In addition, the overall mortality rate in our series — 30 percent — is similar to the rates in other series[21-26] of patients with streptococcal bacteremia (12 to 43 percent); in contrast, the prevalence of both shock (95 percent) and renal failure (80 percent) was markedly higher in our patients. Thus, bacteremia by itself is not sufficient to explain all the complications observed in the present series.

Our patients required intensive fluid replacement, invasive monitoring, and timely surgical debridement.[23,43] The antibiotics used were mainly penicillin and cephalosporins, and no conclusions about optimal antibiotic therapy can be drawn from this small group. Yet, it was in cases of such fulminant forms of streptococcal infection with large numbers of bacteria that Eagle noted, experimentally, the failure of treatment with penicillin.[44] Other approaches to therapy, such as the use of antibiotics that suppress toxin synthesis[45] or immunoglobin treatment, will need to be evaluated.

In summary, the present study describes 20 patients from the Rocky Mountain region who had severe group A streptococcal infection and a toxic shock–like illness. The striking finding in this series was the high frequency with which pyrogenic exotoxin A (scarlet fever toxin type A) was produced by clinical isolates. This finding, together with the complications of acute respiratory distress syndrome, renal impairment, and shock, supports a role for this toxin, at least in part, as a mediator of the streptococcal toxic shock syndrome. Because of the serious nature of this infection, further studies will need to be carried out to determine the prevalence of these strains in our communities and to investigate the mechanisms of shock induced by strains of *S. pyogenes* that produce pyrogenic exotoxin A.

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2

STATE-OF-THE-ART CLINICAL ARTICLE

# Invasive Group A Streptococcus Infections

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**The late 1980s have witnessed the emergence of severe group A streptococcus (GAS) infection; shock, bacteremia, and acute respiratory distress syndrome are common features, and death has been associated with this infection in 30% of patients. Such infections have now been described in all parts of the United States, Europe, and Australia and have occurred predominantly in otherwise healthy adolescents and adults. The characteristic clinical and laboratory features of the streptococcal toxic shock syndrome include deep-seated infection associated with shock and multiorgan failure. Strains of GAS isolated from patients with invasive disease have been predominantly M types 1 and 3, which produce pyrogenic exotoxin A or B or both. In this report, the clinical and demographic features of streptococcal bacteremia, myositis, and necrotizing fasciitis will be presented and compared with those of streptococcal toxic shock syndrome. Current concepts of the pathogenesis of invasive streptococcal infection will also be presented in terms of the interaction between virulence factors of GAS and host defense mechanisms. Finally, new concepts for future treatment of serious streptococcal infections will be proposed.**

Invasive streptococcal infections have been observed for several centuries and include the following unique clinical illnesses: puerperal sepsis, scarlatina maligna, septic scarlet fever, bacteremia, erysipelas, necrotizing fasciitis, gangrene, and myositis. Remarkably, all these forms of streptococcal infections have, until recently, demonstrated marked attenuation in terms of incidence and severity. Although modern medicine has had major impacts on the prevention of rheumatic fever and puerperal sepsis and penicillin is useful in the treatment of group A streptococcus (GAS) infections, the mortality rate for certain GAS infections such as scarlet fever had declined in North America and Europe well before antibiotics were available. Even though some researchers would attribute the decrease in the incidence of serious streptococcal infections to improved socioeconomic conditions, it seems just as likely that in the 1990s we are experiencing enhanced expression of the virulence of GAS. This is a dynamic process that waxes and wanes in its ecological niche, the skin and mucous membranes of humans.

Just as a decrease in the incidence of serious infections was apparent subsequent to the turn of the century, so are we now experiencing more-aggressive GAS infections in a unique population of humans who had hitherto been spared by such severe infections. The course of infection is rapid and frequently fatal in spite of the immunocompetent status of the host. The fulminant nature of these infections is no more impressive than the minor, even trivial, trauma that predisposes the young, healthy host to infection. The speed with which GAS induces local infection, multiorgan failure, and death cannot be matched by any other infectious organism.

A change in the virulence factors of GAS could explain this newfound aggressiveness and could also explain why healthy hosts are attacked. Still, if the explanations were this simple, why have we not witnessed major epidemics of GAS infections due to common-source exposure? Instead we are experiencing an increased incidence of sporadic cases in otherwise healthy, young adults. Similarly, these severe infections are not occurring in immunocompromised patients. Thus if the presence of a new virulence factor alone were sufficient to induce infection, then epidemics would be expected. The susceptibility of the human host must vary even within regional domains. Since individuals without histories of significant bacterial infection are those who are most frequently infected, the answer must lie within the absence of either humoral or cellular immunity to the putative streptococcal virulence factor.

Finally, the interaction between GAS and the human host is an intimate one, and evidence is mounting that the organism has the ability to neutralize and adapt to a variety of host defense mechanisms. Alternatively, cell constituents and toxins of GAS can induce exaggerated host responses in terms of cytokine production or T cell activation. Clinically,

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this unique interaction leads to several presentations of invasive streptococcal disease such as bacteremia, necrotizing fasciitis, myositis, and streptococcal toxic shock syndrome (strepTSS) [1]. The features of each of these entities will be discussed separately.

### Necrotizing Fasciitis

Necrotizing fasciitis is a deep-seated infection of the subcutaneous tissue that results in progressive destruction of fascia and fat but may spare the skin itself. Historically, Pfanner [2] is credited with the first description of what he called necrotizing erysipelas. Several years later Meleney [3] described 20 cases of hemolytic streptococcal gangrene in China, and he argued that this entity was different than erysipelas and should have a different name. These cases, as we now know them, were probably due to GAS, although at that time Meleney only characterized the organism as hemolytic streptococci. In Meleney's series [3], seven of 17 patients for whom blood cultures were performed had bacteremia due to hemolytic streptococci, and the only organism isolated from the site of infection (or reported) was hemolytic streptococcus. It is of interest that all age groups were affected and that the mortality rate was 20%. Subsequently, necrotizing fasciitis has become the preferred term since bacteria other than streptococci, such as *Clostridium perfringens*, *Clostridium septicum*, and *Staphylococcus aureus*, can produce a similar pathologic process (see table 1).

Meleney [3] described streptococcal gangrene as characteristically beginning at the site of trivial or inapparent trauma. Within 24 hours of the initial lesion—which frequently appears as only mild erythema—swelling, heat, erythema, and tenderness develop extensively and rapidly spread proximally and distally from the original focus. During the next 24–48 hours, the erythema darkens, changing from red to purple and then to blue, and blisters and bullae form that contain clear yellow fluid. On the fourth or fifth day, the purple areas become frankly gangrenous. From the seventh to the 10th day, the line of demarcation becomes sharply defined, and the dead skin begins to separate at the margins or breaks in the center, revealing extensive necrosis of the subcutaneous tissue. Up until this time, the patient continues to be febrile and becomes increasingly prostrated and more emaciated. In more-severe cases, the process advances rapidly until several large areas of skin have become gangrenous, and the intoxication renders the patient dull, unresponsive, mentally cloudy, or even delirious. Subsequently, the patient may develop metastatic abscesses, bronchopneumonia, or lung abscess [3].

**Table 1.** Characteristics of patients with necrotizing fasciitis due to GAS.

| Year [reference] | No. of cases | Age of patients (y) | Predisposing factors: Underlying disease | Predisposing factors: Events leading to infection (% of patients) | Occurrence of shock (% of patients) | Causative bacteria (% of patients) | Mortality rate (%) |
|---|---|---|---|---|---|---|---|
| 1924 [3] | 20 | NG but young, healthy | None | Minor trauma | Rare | Hemolytic streptococci | 20 |
| 1970 [4] | NG | NG* | Diabetes; peripheral vascular disease | Minor trauma (80); surgical procedures (20) | 11 | Hemolytic streptococci (44.5), *Staphylococcus aureus* (44.5), gram-negative organisms (11.0%) | 30 overall, 63 in diabetics† |
| 1952 [7] | 22 | 47 (mean)‡ | None | Stab wounds, gunshot wounds, appendectomy, contusions, abrasions, splinters | 43 | *Staphylococcus* species (88), hemolytic streptococci and other organisms | 9<br>20 |
| 1971 [5] | 7 | 41 (mean)§ | Rheumatoid arthritis, diabetes | Orthopedic procedures | 57 | GAS | 57 |
| 1982 [6] | 9 | 61 (mean) | Diabetes, cachexia, peripheral vascular disease, cirrhosis; corticosteroid therapy | Minor trauma | 77 | GAS | 55 |
| 1989 [1] | 20 | 20–40 | None | Minor trauma | 100 | GAS | ~30 |

NOTE. NG = not given.

* Mortality among patients >50 years of age was 67% (18 of 44 patients were >50 years of age).

† All deaths occurred in patients >50 years of age.

‡ All patients <30 y of age had experienced stab wounds, gunshot wounds, or appendectomy.

§ Mean age of these patients is skewed somewhat by a 2-year-old child who underwent an operation for congenital dislocation of the hip.

It should be remembered that Meleney's description of hemolytic streptococcal gangrene was published in 1924, well before the advent of antibiotics [3]. In fact, he was the first to advocate aggressive "bear scratch" fasciotomy and debridement. Using this approach as well as irrigation with Dakin's solution, he observed mortality rates as low as 20%. In contrast, data from subsequent reports written during 1950–1980 suggest that mortality rates >50% are common even with antibiotic use and aggressive surgical debridement. Table 1 lists the comparative characteristics of patients with streptococcal gangrene and necrotizing fasciitis that were documented in different reports.

Necrotizing fasciitis is caused by a variety of etiologic agents, including hemolytic streptococcus, *S. aureus*, and enteric organisms (e.g., *Clostridium* species alone or in combination). For example, of the 44 patients in the study by Rea and Wyrick [4], 19 had cultures positive for *S. aureus* and 19 had cultures positive for hemolytic streptococcus; 14 had cultures positive for both *S. aureus* and hemolytic streptococcus. In that study, 80% of patients had sustained minor trauma and 20% developed infection following surgical procedures. In addition, most patients had either diabetes or peripheral vascular disease. The patients' ages were not mentioned, although 18 of the 44 patients were >50 years of age; among these patients the mortality rate was 63% in spite of antibiotic use and surgery. In an additional study of necrotizing fasciitis, *S. aureus* was isolated from 88% of patients, even though the mortality rate among patients was only 8.7%. It is of interest that all patients <30 years of age had experienced stab wounds, gunshot wounds, or appendectomy.

Similarly, the study by Quintiliani and Engh [5] of overwhelming GAS bacteremia involved seven patients undergoing orthopedic procedures who developed severe streptococcal soft-tissue infections; overall, 57% of the patients died. The mean age of the patients was 41 years, although this is misleading since one of the patients was only 2 years of age. Several patients had either peripheral vascular disease or diabetes. Finally, in the study by Aitken et al. [6], the mean age of the patients was 61 years, and their infections developed following minor trauma. The mortality rate, in spite of antibiotic use and surgery, was 55%, even though most of the patients had diabetes, cachexia, peripheral vascular disease, or cirrhosis or were receiving corticosteroids.

If one compares these reports [3–7] with descriptions of cases of strepTSS [1], several differences are apparent. First, recent cases have been reported mainly in young, healthy individuals with no underlying disease who sustain some minor trauma to an extremity. Previous reports describe older patients with multiple medical problems [3–7]. Although Meleney's patients (who were in China) were young, healthy individuals, the mortality rate (20%) [3] among these patients was lower (30%–60%) [4–6] than that of recently described cases. In addition, the lower mortality reported by Meleney occurred at a time when antibiotics were not yet available [3]. Perhaps the higher mortality rates documented in subsequent reports, in spite of antibiotic use, could be related to the patients' underlying diseases, older age, and major traumatic experiences, e.g., orthopedic procedures, gunshot wounds, stab wounds, and major intraabdominal surgery. Another reason for the increased severity of present cases of strepTSS in terms of shock, multiorgan failure, and mortality (in spite of the absence of underlying disease, younger age, and use of antibiotics) could be the emergence of increased virulence of GAS itself [1].

## Streptococcal Myositis

Streptococcal myositis is an extremely uncommon GAS infection. Adams et al. [8] documented only 21 cases that had been reported from 1900 to 1985, and Svane [9] found only four cases among >20,000 autopsies. In our report of 20 patients with invasive GAS infection [1], one had myositis, three had myositis as well as necrotizing fasciitis, and five had necrotizing fasciitis alone. Recently, deep soft-tissue infections, such as necrotizing fasciitis and myositis, have also been described in reports from Norway [10] and Sweden [11]. Translocation of GAS from the pharynx to the muscle site must occur via hematogenous spread since penetrating trauma is usually not sustained. Most reported cases developed spontaneously or were secondary to very minor blunt trauma or to muscle strain, and most patients had not experienced symptomatic pharyngitis or tonsillitis [1, 8–13]. Severe pain may be the only presenting symptom, and the early physical findings may be only swelling and erythema, even though patients may rapidly develop muscle compartmental syndromes [1, 8–13]. In most cases a single muscle group may be involved; however, because patients are frequently bacteremic, multiple sites of myositis or abscess can occur [1, 8]. Distinguishing streptococcal myositis from spontaneous gas gangrene due to *C. perfringens* or *C. septicum* [14] may be difficult, although the presence of crepitus or gas in the tissue would favor clostridial infection [12]. Necrotizing fasciitis is easily distinguished from myositis anatomically by means of surgical exploration or incisional biopsy. Clinical features of both conditions overlap, and patients may have symptoms of both necrotizing fasciitis and myositis [1, 8]. In published reports, the case-fatality rate of necrotizing fasciitis is between 20% and 50%, whereas that of GAS myositis is between 80% and 100% [1, 8–13]. Aggressive surgical debridement is of extreme importance because of the poor efficacy of penicillin described in human cases [1, 8, 9, 12, 13] as well as in experimental streptococcal models of myositis [15, 16] (see section on antibiotic efficacy).

## Malignant Scarlet Fever

Osler [17] described three types of malignant scarlet fever: anginose, hemorrhagic, and atactic. The anginose form was basically membranous exudation of the throat, with necrosis

of the soft tissues of the pharynx and soft palate. Exudation could continue into the trachea, bronchi, eustachian tubes, and middle ear. He noted that in some cases necrosis and sloughing of tissue about the tonsils were so severe that necrosis of the carotid artery occurred with fatal hemorrhage. Osler did not specify the time course of this form although Holt [18] subsequently stated that "the duration of the symptoms in fatal cases is from six to fourteen days." In the second variety, hemorrhages into the skin, hematuria, and epistaxis occurred. "Enfeebled children" were the group most commonly associated with this form, and death, when it occurred, was usually within the first 2–3 days of illness [17, 18]. The third form described by Osler was atactic scarlet fever, in which children presented with the characteristics of acute intoxication. The disease began with great severity, causing high fever, extreme restlessness, headache, and delirium. Patients' temperatures were frequently between 107°F and 108°F, and Osler stated that ". . . rare cases have been observed in which the thermometer has registered even higher." Convulsions, coma, severe dyspnea, and rapid feeble pulses were the most common presenting signs. Death occurred within 24–48 hours [17].

Weaver [19] combined all these definitions into the following groups: mild, moderate, toxic, and septic. Thus, benign scarlet fever could be either mild or moderate, and the fatal or malignant form of scarlet fever could be either septic or toxic. The toxic cases invariably began with a severe sore throat, marked fever (107°F–108°F), delirium, skin rash, and painful cervical lymph nodes [17]. In severe toxic cases (similar to the malignant scarlet fever described by Osler [17] and Rotch [20]), fulminating fevers to 107°F–108°F, pulse rates of 130–160, severe headache, delirium, convulsions, little if any skin rash, and death within 24 hours were the usual findings. These cases occurred before the advent of antibiotics, antipyretics, and anticonvulsants. The septic cases were similar to those described by Wood [21] as scarlatina anginosa and by Osler [17] as the anginose form of scarlet fever. In septic cases, local invasion of the soft tissues of the neck was the prominent feature along with subsequent upper-airway obstruction, otitis media with perforation, profuse mucopurulent drainage from the nose, bronchopneumonia, and death. The clinical characteristics of the various types of scarlet fever are listed in table 2. Note that necrotizing fasciitis and myositis were not described in association with scarlet fever, the only exception being locally invasive infection of the soft tissues of the neck as a complication of pharyngitis.

### Bacteremia

Bacteremia associated with GAS pharyngitis is uncommon, and even during scarlet fever it occurs in only 0.3% of febrile patients [22]. In the past, streptococcal bacteremia occurred most commonly in very young individuals and in

**Table 2.** Comparison of the clinical characteristics of severe GAS infections

| Type of GAS infection | Other names | Clinical presentation | Complications | Years of age (% of patients) | Predisposing factors |
|---|---|---|---|---|---|
| Scarlet fever | Benign scarlet fever, moderate scarlet fever, scarlet fever simplex | Fever, pharyngitis, scarlatina rash, desquamation | Late rheumatic fever or glomerulonephritis, death rare | <10 (90) | None |
| Septic scarlet fever | Scarlatina anginosa, malignant sore throat, garrotillo, morbus strangulatoris, ulcerative angina | Scarlet fever with local suppuration and invasion of deeper structures | Otitis sinusitis, meningitis, airway obstruction, bacteremia, cavernous vein thrombosis | <10 (90) | Preantibiotic era |
| Toxic scarlet fever | Malignant scarlet fever, atactic scarlet fever | Scarlet fever with hyperpyrexia and either neurological complications or cardiovascular collapse, rash evanescent or absent | Convulsions, coma, sudden death | <10 (90) | Preantibiotic era, lack of anticonvulsants, antipyretics, and iv fluids |
| Bacteremia | · · · | Fever, bacteremia, shock | DIC, shock, death | <1 and >75 | Diabetes, burns, newborns, institutionalized elderly |
| Myositis, necrotizing erysipelas, streptococcal gangrene | Necrotizing fasciitis | Fever, bullous skin lesions, renal failure | Renal failure, shock, death | | Diabetes, severe trauma surgery |
| StrepTSS | · · · | Fever, shock, rash or bullous skin lesion, early renal failure, thrombocytopenia | ARDS, renal failure, loss of limb, death | Any age, but the majority are 20–60 (· · ·) | Minor trauma, surgery, viral illness; nonsteroidal therapy (?) |

NOTE. Ellipses = data not available. DIC = disseminated intravascular coagulation, ARDS = acute respiratory distress syndrome

the elderly [23–32]. Among children, predisposing factors other than scarlet fever include burns, varicella, malignant neoplasm, immunosuppression, and age of <2 years [23–32]. In patients with scarlet fever, the pharynx is the most common source of GAS, and frequently such patients have complications that include extension of infection into the sinuses, peritonsillar tissue, or mastoids (septic scarlet fever or the anginose form of scarlet fever) [19, 20]. The integument is the most common source of GAS in patients with burns and varicella; in the latter patients, bacteremia occurs later as the vesicles are crusting and drying up [22]. The least common source of bacteremia in children is the lower respiratory tract, and bacteremia from this source may be associated with prior viral infections. For example, secondary bacterial pneumonia has occurred in ~3.0% of patients with varicella and invariably occurs in children <7 years of age [22]; in adults GAS pneumonia complicating varicella is rarely found, although primary varicella pneumonia occurs commonly. Among the children with varicella studied by Bullowa and Wischik [22], GAS bacteremia occurred in ~0.5% of patients.

In elderly patients the source of GAS infection is invariably the skin and is associated with cellulitis or erysipelas [23–32]. GAS sepsis in the elderly has also been associated with diabetes, peripheral vascular disease, malignancy, and use of corticosteroids [23–32]. Epidemics of GAS bacteremia associated with soft-tissue infection among the elderly have been reported in the past and more recently by the Centers for Disease Control (Atlanta) [33]. In most reports (see table 3), the mean age of patients with bacteremia was between 50–60 years. Not surprisingly, mortality rates of 35%–80% have been described among this patient population [23–32].

In the past, the occurrence of GAS bacteremia was rare in individuals 14–40 years of age [23–32]. In the distant past, puerperal sepsis accounted for most of the cases of bacteremia in this age group [23]. Today such cases still occur but are rare, largely because of the epidemiological and "infection control" policies put forth by Semmelweiss in Europe and Holmes in the United States. Intravenous drug abuse has emerged as a leading cause of GAS bacteremia in this age group in the modern era (table 3) [29, 32]. In contrast, in our study of invasive GAS infection in the Rocky Mountain area, only 10% of patients had a history of intravenous drug abuse, and the greatest prevalence of GAS bacteremia occurred in previously healthy adolescents and young adults. This finding has also been substantiated by pediatricians [33] and by public health officials in England [34], Norway [10], the United States [35], and Sweden [11]. Martin and Hoiby [10]

**Table 3.** The clinical and epidemiological features of GAS bacteremia during 1937–1989

| Year [reference] | No. of patients | Years of age (% of patients) | Site or type of infection (% of patients) | Presence of underlying disease or condition (% of patients) | No. of patients with shock | Mortality rate (%) | Causative organism |
|---|---|---|---|---|---|---|---|
| 1937 [23] | 69 | 0–20 | Throat, ear, mastoid | 0 | ... | 55 | GAS |
| | 41 | 20–40 | Puerperal sepsis | 0 | ... | 56 | GAS |
| | 61 | >40 | Cellulitis, erysipelas | 0 | ... | 80* | |
| 1969 [24] | 19 | >50 | Soft tissue (>50) | 74 | ... | 57 | GAS |
| 1971 [6] | 7 | 41 (mean)† | Soft tissue (100) | 100 | ... | ... | |
| 1988 [25] | 40 | 53 (mean) | Soft tissue (58), respiratory tract (20) | 52† | 39 (RF in 11 of 40) | 35 | GAS |
| 1970 [26] | 49 | 54 (mean) | Soft tissue (33), respiratory tract (33), unknown (33) | 100‡ | 18 | 45‡ | GAS |
| 1973 [27] | 44 | >60 | Soft tissue (60) | 55 | NS | 7 | GAS |
| 1981 [28] | 58 | 59 (mean) | Soft tissue (72) | 50 | NS | 22 | GAS |
| 1985 [29] | 40 | 32.6 (mean) | Soft tissue (68), endocarditis (27) | 100§ | 20 | 5 | GAS |
| 1988 [30] | 67 | >50 (53)<br>20–40 (31)<br><20 (16) | Soft tissue (~60)<br>No site identified (37) | ~30 | ... | 48 | GAS‖ |
| 1989 [31] | 20 | <11 (35)<br>>55 (55)<br>19–22 (10) | Pneumonia (30) | 64 | ... | 35 | GAS |
| 1991 [32] | 58 | <20 (9)<br>20–40 (34)#<br>>40 (57) | Soft tissue (72) | 28 | NS | | GAS |

NOTE. Ellipses = data not given, RF = renal failure, NS = no shock.

* All patients underwent orthopedic procedures.

† Forty percent of patients had nonfatal systemic disease, and 15% had fatal underlying disease.

‡ All patients had major underlying diseases.

§ All patients were intravenous drug abusers.

‖ Forty-five of 67 cases were due to M type 1, 3, 4, or 12. These strains accounted for 22 to 28 deaths.

# Mean age of intravenous drug abusers was 33 years. Among all other patients, the mean age was 55 years.

have comprehensively demonstrated that the prevalence of GAS bacteremia in Norway has increased in all age groups, but the greatest increase (600%–800%) has been in adolescents and young adults [10]. Thus, the demographics of patients with invasive streptococcal infections have changed dramatically in the past 4–6 years [1, 10, 11, 33–35].

## Streptococcal Toxic Shock Syndrome

Recently, cases of severe invasive GAS infections have been reported with increasing frequency, predominantly in North America and Europe [1, 10, 11, 33–40]. Such cases are particularly dramatic since in previous years the frequency, severity, and complications of GAS infections had decreased. In the late 1980s, reports of invasive GAS infections associated with bacteremia, deep soft-tissue infection, shock, and multiorgan failure (see case definition in table 1) began to appear. Since 1985 >30 reports or abstracts have documented the appearance of aggressive streptococcal infections associated with bacteremia and shock in all age groups [1, 10, 11, 33–40]. Patients between the ages of 20 and 50 years are most commonly afflicted, and such patients frequently do not have predisposing underlying diseases [23–32]. This is in sharp contrast to the previous reports of GAS bacteremia, in which patients were either <10 years of age or >60 years of age and in which most patients also had underlying diseases such as cancer, renal failure, leukemia, or severe burns or were receiving therapy with corticosteroids or other immunosuppressive drugs [23–32]. Although younger, healthier individuals are most commonly infected, bacteremia, severe soft-tissue infection, shock, acute respiratory distress syndrome (ARDS), and renal failure are common complications of severe invasive GAS infection, and reports indicate that overall 30% of patients with this infection have died in spite of aggressive modern treatments.

### Acquisition of GAS

The portal of entry of streptococci is the skin or mucous membranes, although a definite portal of entry cannot be ascertained in 45% of cases [3]. Rarely, patients with symptomatic pharyngitis develop strepTSS as a complication. Similarly, most women who develop strepTSS have no history of vaginal infection. Thus, currently the mucous membranes serve more as a source of bacteria than as a site of symptomatic local infection. Suction lipectomy, hysterectomy, vaginal delivery, bunionectomy, and bone pinning have also provided a portal of entry in many cases (author's unpublished observations). Rarely, the organism has been acquired through person-to-person contact. For example, a paramedic developed strepTSS after resuscitating a young child dying of strepTSS [41]. In one instance, two patients who had undergone suction lipectomy performed by the same surgeon on the same day developed strepTSS within 24–48 hours of the procedure, and one patient died (author's unpublished observations). For the most part, these infections have occurred sporadically and have not been associated with clusters of cases or minor epidemics. Most commonly, the streptococcal infection begins at a site of minor local trauma that frequently does not result in a break in the skin [1]. For example, numerous cases have developed within 24–72 hours of minor nonpenetrating trauma that results in hematoma or a deep bruise (e.g., to the calf), and some cases have even developed following muscle strain [1]. Viral infections such as varicella and influenza have provided a portal of entry in other cases [1]. Primary varicella in children and young adults is also associated with strepTSS, and the portal of entry of streptococci is usually the varicella vesicle, although in children with GAS pneumonia it is likely the oropharynx.

In our study [1], a virus-like prodrome suggestive of influenza preceded the onset of strepTSS by several days in adults. Although influenza has only rarely been documented, many patients had received therapy with amantadine hydrochloride during this early phase of the illness. It is of interest that such patients rarely develop GAS pneumonia, and most of these patients present with deep-seated soft-tissue infection instead. In some cases the use of nonsteroidal antiinflammatory agents may have either masked the presenting symptoms or predisposed the patient to more-severe streptococcal infections and shock. Among the patients who received such treatment, the initial clinical diagnosis was frequently deep-vein thrombophlebitis. In such cases the diagnosis of deep soft-tissue infection was frequently delayed because of the lengthy process of performing Doppler examinations and obtaining venograms. Thus, antimicrobial therapy was delayed and frequently not initiated until renal failure, ARDS, or shock became manifest.

### Symptoms of StrepTSS

Pain, the most common initial symptom of strepTSS, occurred in 85% of cases in our study [1] and was abrupt in onset and very severe. In some cases pain was not associated with tenderness or physical findings. Frequently, the patient's pain was so severe that parenteral narcotic analgesics were prescribed. The pain most commonly involved an extremity but also mimicked symptoms and pain associated with peritonitis, pelvic inflammatory disease, acute myocardial infarction, or pericarditis [1]. Before the onset of pain, 20% of patients had an influenza-like syndrome characterized by fever, chills, myalgia, and diarrhea.

### Physical Findings of StrepTSS

In our study [1], fever was the most common presenting sign, although on admission to the hospital 10% of patients presented with profound hypothermia and shock. Confusion was noted in 55% of patients, and in some patients it progressed to coma or combativeness. On admission 80% of pa-

tients had tachycardia and 55% had systolic blood pressure of <110 mm Hg (table 4). Although 45% of patients had normal blood pressure (systolic pressure, >110 mm Hg) on admission, all of these patients developed hypotension within the subsequent 4 hours. Eighty percent of patients developed evidence of soft-tissue infection, and localized swelling and erythema were the most common findings at the time of admission. An ominous sign was the progression of soft-tissue swelling to formation of vesicles and then bullae, which took on a violaceous or bluish coloration. Soft-tissue infection evolved to necrotizing fasciitis or myositis in 70% of cases and in these cases surgical debridement, fasciotomy, or amputation was required. For the 20% of patients for whom there was no evidence of soft-tissue infection, a variety of clinical presentations were observed; these included endophthalmitis, myositis, perihepatitis, peritonitis, myocarditis, and overwhelming sepsis.

**Table 4.** Clinical summary of StrepTSS.

| Category, characteristic | Value |
|---|---|
| Physical findings (% of patients with finding) | |
| Fever >38°C | 70 |
| Confusion | 55 |
| Heart rate >100 | 80 |
| Hypotension | 100 |
| Cutaneous signs | |
| Swelling | 10 |
| Swelling and erythema | 65 |
| Bullae | 5 |
| Desquamation (late) | 20 |
| Results of laboratory tests* | |
| White blood cells (per mm$^3$) | 11,765/· · · |
| Immature granulocytes (%) | 43/· · · |
| Platelets (per mm$^3$) | 216,000/129,000 |
| Creatinine (mg/dL) | 2 5/3 4 |
| Calcium (mg/dL) | 8.1/6 6 |
| Albumin (g/dL) | 3 3/2 3 |
| Creatine phosphokinase (IU) | 3,000/100,000 |
| Complication (% of patients with complication) | |
| Shock | 95 |
| Acute respiratory distress syndrome | 55 |
| Renal impairment | 80 |
| Irreversible | 10 |
| Reversible | 70 |
| Sepsis | 60 |
| Death | 30 |

NOTE. Early symptoms of strepTSS are vague and involve a virus-like prodrome, pain and redness of an extremity, which are usually severe; and confusion

* Mean values on admission/at 48 hours

### Laboratory Test Results for Patients with StrepTSS

Evidence of renal involvement was apparent at the time of admission by the presence of hemoglobinuria and serum creatinine levels that were >2.5-fold the normal value (table 4). By 48 hours (see table 4), the measured creatinine levels had increased steadily to 3.5-fold the normal value. For every patient who presented with an elevated serum creatinine level, the results of testing the urine for hemoglobin (Hemastix) were also positive. The serum albumin level was 3.3 g/dL (mean value) on admission and dropped to 2.3 g/dL by 48 hours. Hypoalbuminemia was associated with hypocalcemia on admission and throughout the hospital course. The cause of hypocalcemia was unknown but was in part related to concomitant hypoalbuminemia; however, since the ionized calcium level was also low [1], other mechanisms must have been operative. The serum creatine kinase level was useful in detecting the presence of deeper soft-tissue infections, and when the level was elevated or rising, there was a good correlation with necrotizing fasciitis or myositis [1].

The initial laboratory studies demonstrated mild leukocytosis (mean leukocyte count, 12,000 cells/mm$^3$) and a profound left shift (see table 4). The mean percentage of immature neutrophils (including band forms, metamyelocytes, and myelocytes) was 43%. The mean platelet count was normal on admission but dropped to 129,000 cells/mm$^3$ within 48 hours [1]. Initially, the mean hematocrit values were normal for the altitude at which they were measured but dropped dramatically by 48 hours (i.e., from 43% to 29%).

### Bacteriologic Cultures

Cultures of blood were positive for GAS in 60% of cases, and those of specimens from the site of infection were positive for GAS in 95% of cases [1]. The types of infection included peritonitis, necrotizing fasciitis, myositis, cellulitis, empyema, endophthalmitis, suppurative thrombophlebitis, meningitis, and infections of a bone or joint or the myometrium.

### Clinical Course

Shock was apparent at the time of admission or within 4–8 hours in virtually all patients. In 10% of patients, the systolic blood pressure returned to normal 4–8 hours after administration of antibiotics, albumin, and electrolyte solutions containing salts or dopamine (see table 4). In other patients shock persisted. Similarly, renal dysfunction progressed or persisted in all patients for 48–72 hours in spite of treatment, and several patients required dialysis for 10–20 days [1]. In all patients who survived, serum creatinine levels returned to normal within 4 to 6 weeks. Renal dysfunction preceded shock in many patients and was apparent early in the course of shock in all other patients. ARDS occurred in 55% of patients and generally developed after the onset of hypotension [1]. The severity of ARDS was such that supplemental oxygen, intubation, and mechanical ventilation were necessary for 90% of patients who developed this syndrome [1]. Sixty percent of patients were bacteremic, and overall 30% of patients died [1]. Morbidity was also high; 13 patients underwent major surgical procedures, which included fasciotomy,

surgical debridement, exploratory laparotomy, intraocular aspiration, amputation, and hysterectomy [1].

### Characteristics of Clinical Isolates of GAS

Our study [1] demonstrated that M types 1 and 3 of GAS were the most common isolates from patients with shock and multiorgan failure. Studies in conjunction with the World Health Organization Streptococcal Reference Laboratory [42], the Centers for Disease Control [35], the Canadian Centers for Disease Control [43], and the British Reference Laboratories in Colindale [34] and reports from Sweden [11], Norway [10], and the German Democratic Republic [44] also have documented that M types 1 and 3 as well as types 12 and 28 are most frequently isolated from such patients. Our study [1], a more recent report [42] of a larger series of patients with invasive streptococcal infections, and studies involving different kinds of streptococcal infection have demonstrated that pyrogenic exotoxin A and/or exotoxin B is found in the majority of patients with severe infection. Outbreaks of GAS infection in Norway [10], Sweden [11], and Great Britain [34] have been primarily due to M type 1 strains of GAS that produce pyrogenic exotoxin B.

### Current Hypotheses Regarding Mechanisms of Shock and Tissue Destruction Caused by Virulent GAS

Some infections associated with strains of GAS that produce streptococcal pyrogenic exotoxin A (SPEA) are characteristically associated with shock, ARDS, renal failure, and tissue destruction [1]. Pyrogenic exotoxins induce fever in humans and animals and also participate in shock by lowering the threshold for exogenous endotoxin [45–47]. SPEA and streptococcal pyrogenic exotoxin B (SPEB) induce human mononuclear cells to synthesize not only tumor necrosis factor-$\alpha$ (TNF-$\alpha$) [48, 49] but also interleukin-1$\beta$ [49] and interleukin-6 [49], thereby suggesting that TNF-$\alpha$ could mediate fever, shock, and tissue injury observed in patients with strepTSS [1].

M protein contributes to invasiveness through its ability to impede phagocytosis of streptococci by human polymorphonuclear leukocytes [50]. Conversely, type-specific antibody to M protein enhances phagocytosis [50]. Following infection with a particular M type of GAS, specific antibody confers resistance to challenge with viable GAS of that M type [50].

Could strepTSS be related to the ability of SPEA or M protein type 1 or 3 to act as "super antigens" [51]? There are data to suggest that SPEA and a number of staphylococcal toxins (toxic shock syndrome toxin 1 and staphylococcal enterotoxins A, B, and C) can stimulate T cell responses through their ability to bind to both the class II major histocompatibility complex of antigen-presenting cells and the $V_\beta$ region of the T cell receptor [51]. Thus, direct stimulation of helper T cells can occur in the absence of classic antigen processing. The net effect would be to induce T cell stimulation with production of cytokines that are capable of mediating shock and tissue injury. Recently, Kotb et al. [52] have shown that a digest of M protein type 6 can also stimulate T cell responses by this mechanism.

Finally, Cleary et al. [53] have provided evidence that several virulence factors of GAS (M protein, $C_5$ peptidase, etc.) may be located within a specific locus on the genome and that their expression is under the control of an upstream DNA sequence or regulon. Factors that affect the regulon could markedly increase or decrease the expression of virulence factors of GAS.

The interaction between these microbial virulence factors and an immune or nonimmune host determines the epidemiological factors, clinical syndrome, and outcome of infection. Figure 1 illustrates the potential outcomes following the contact of immune and nonimmune individuals with SPEA-producing strains of M type 1 GAS. This model explains (1) why epidemics have not materialized and (2) why different clinical manifestations can occur in the same community. We conclude that M types 1 and 3 likely facilitate invasiveness of the organisms on the basis of the antiphagocytic properties of M proteins of streptococcal groups classified by Lancefield. Although the antiphagocytic properties of these specific M types (type 1 and type 3) have not been investigated, such studies would be of major importance. The initial encounter between a virulent M type 1 or 3 strain and the host will not result in infection if the host has circulating or mucosal antibody to the specific M type. A less invasive strain (such as M type 4) that produces pyrogenic exotoxin A, B, or C could cause local pharyngitis and subsequent scarlet fever if the host did not have antibody to either M protein type 4 or pyrogenic toxin.

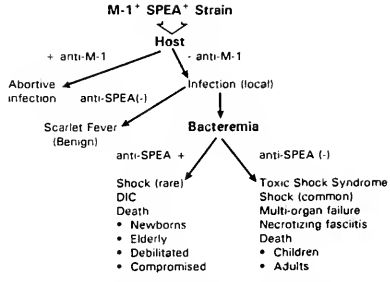


**Figure 1.** Pathogenesis of scarlet fever, bacteremia, and toxic shock syndrome. M-1+ SPEA+ = a GAS strain that contains M protein type 1 and pyrogenic exotoxin A (SPEA); +anti-M-1 = the presence of antibody to M protein type 1; −anti-M-1 = the absence of antibody to M protein type 1; anti-SPEA + = antibody to SPEA; and DIC = disseminated intravascular coagulation.

We hypothesize that once invasion of mucosal or epithelial barriers by GAS of M type 1 or 3 has occurred in a host without specific antibody to M protein, tissue invasion and possibly bacteremia will occur. If the invading strains also produce pyrogenic exotoxins (A or B but probably not C), then their expression results in shock, multiorgan failure, and tissue destruction. The latter scenario would be expected in patients who lack specific antibody to the pyrogenic exotoxin produced by the invading strain. That this hypothesis is correct is supported by the recent finding of Holm and Bergholm [11]; these researchers found that among patients in Sweden who had invasive streptococcal infection caused by M type 1 strains producing SPEB, only those who lacked antibody to pyrogenic exotoxin B developed shock. Conversely, we hypothesize that in patients who have preexisting antibody to one or all pyrogenic exotoxins, GAS strains might cause bacteremia alone without soft-tissue infection, shock, or multiorgan failure. In this case, the outcome would be dependent upon underlying disease, the patient's age, and iatrogenic immunosuppression.

## Current and Future Directions in Therapy for Severe GAS Infections

Penicillin, erythromycin, and clindamycin are the drugs of choice for the treatment of GAS infections. Yet for patients with severe infections (such as necrotizing fasciitis or myositis) in whom large numbers of streptococci are found, penicillin's remarkable efficacy is diminished. Eagle's study [15] and our study [16] suggest that the failure of penicillin in this setting is due to the slower growth rate of streptococci at large inoculum sizes. Clinically such numbers of streptococci are probably only encountered in overwhelming sepsis, necrotizing fasciitis, or myositis. Other antibiotics that are more effective than penicillin in experimental models of myositis include, in decreasing order of efficacy, clindamycin, erythromycin, and ceftriaxone [16, 54]. The reasons that these agents are more effective have not been established but may be due in part to the suppression of M protein synthesis or toxin production by protein synthesis inhibitors such as clindamycin and erythromycin [55]. In the United States erythromycin resistance is low (<4.0%), although in Japan it reached 72% in 1975. The reason for ceftriaxone's modestly greater efficacy in this setting is not known but could be due to the greater affinity of ceftriaxone for streptococcal penicillin-binding proteins.

In situations where infection is well established, prompt surgical drainage, debridement, fasciotomy, or amputation may be necessary. If sufficient quantities of toxin have been produced and absorbed to induce shock-producing quantities of cytokines, the mortality is high even in the younger, healthier group of patients who seem to be most susceptible. Thus, early recognition of infection and prompt antibiotic therapy are mandatory. Future strategies will be directed to the diagnosis of the specific stage of strepTSS, i.e., stage I, localized infection; stage II, circulating toxins; stage III, circulating cytokines; and stage IV, shock and multiorgan failure. The therapeutic strategy will be (1) to destroy the organism at stage I with antimicrobial agents, preferably ones that suppress toxin production; (2) to neutralize the circulating toxin at stage II with monoclonal antibodies to specific toxins or possibly gamma globulin; and (3) to neutralize the circulating cytokines at stage III. Thus, new antibiotics must be studied in severe types of human infection, neutralizing monoclonal antitoxin antibodies must be developed, and clinical investigations involving antibodies to as well as receptor antagonists for TNF-$\alpha$ and interleukin-1 should be initiated.

*Editor's note.* The author is interested in receiving strains of GAS isolated from patients with invasive streptococcal disease and also in obtaining tissue specimens or serum samples for measurement of cytokine levels. Please call (208) 389-7964 for information and send specimens to the following address: Infectious Diseases (T-109), Veterans Affairs Medical Center, 500 West Fort Street, Boise, Idaho 83702.

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Mr. TOWNS. I call the second panel, Dr. Dale Morse, New York State epidemiologist, and Dr. Edward Kaplan, head of the World Health Organization laboratory in the University of Minnesota.

I remind you that your entire witness statement will be included in the record. We would like for you to summarize within 5 minutes so the Members will have an opportunity to raise questions with you.

Dr. Kaplan, I guess for continuity, why don't we begin with you.

**STATEMENT OF EDWARD L. KAPLAN, M.D., PROFESSOR OF PEDIATRICS, UNIVERSITY OF MINNESOTA MEDICAL SCHOOL, AND PROFESSOR, DIVISION OF EPIDEMIOLOGY, UNIVERSITY OF MINNESOTA SCHOOL OF PUBLIC HEALTH, AND HEAD, WORLD HEALTH ORGANIZATION COLLABORATING CENTER FOR REFERENCE AND RESEARCH ON STREPTOCOCCI**

Dr. KAPLAN. Thank you, Mr. Chairman. I am very grateful for the invitation and the opportunity to meet with you this morning.

I am Edward Kaplan. I am a pediatrician and currently professor of pediatrics at the University of Minnesota Medical School and also professor in the School of Public Health's Division of Epidemiology.

Furthermore, I come to you as head of the World Health Organization, Streptococcal Reference Laboratory at the University of Minnesota, which is probably, without asking what the other laboratory was that Dr. Broome referred to, the other one that can type these organisms in the United States at the present time.

I have worked in the area of streptococcal infections in epidemiology and so on for almost 30 years, and bring to you not only the laboratory perspective, but in addition, that of a clinician who has taken care of patients.

And since streptococcal infections have been referred to by someone as an occupational disease of school children, as a pediatrician I feel particularly appropriate to be here, and for that reason I am very grateful.

A lot has been said about this problem this morning, and things which I had intended to say—but rather than repeat those for you, I would like to touch on some of the things I think, Mr. Chairman, are important.

I think group A streptococcal infections continue to constitute another of the very common infectious diseases which continue to have the potential for causing severe trouble, both from a medical as well as a public health point of view. These are important and have continued to be important, and I think we have to understand the background of these infections in order to understand what has happened recently.

I think one of the most important issues is that most streptococcal infections are not severe infections. In fact, it has been estimated, recent figures that I have seen, that there are about 4 million cases of streptococcal sore throat in the United States yearly. Those are soft data, admittedly, but it gives you some idea of the magnitude of what we are dealing with.

It is not these uncomplicated infections that have had us concerned over the years. It is their consequences, particularly diseases like rheumatic fever and glomerulonephritis, which used to

be called Bright's Disease. It is the complications of these diseases that cause a great deal of concern. For example, in the U.S. Navy alone during the Second World War, there were some 20,000 cases of acute rheumatic fever, it has been estimated.

This concern was brought very well, I think, to the medical population, to medical practitioners and to the public, and for these diseases, these complications tended to disappear since the Second World War. We have had very few cases up to about 10 years ago. We have no complete understanding of why this occurred but there are some suggestions.

For example, in upstate New York, in Rochester, in Monroe County, a throat culture program there over the last 20 years showed no decrease in the number of uncomplicated streptococcal infections, but when they looked at the incidence of rheumatic fever and glomerulonephritis, this fell off remarkably between the mid-1960's and mid-1980's, and maybe we became a little complacent and forgot this infection has great potential for causing problems.

It still came back to us. For example, there have been almost 275 cases of acute rheumatic fever noted in Salt Lake City, UT, between 1985 and 1992, a city where they were seeing three to six cases per year in the previous years.

Recently, within the last month or two, I am aware of at least two other small outbreaks of acute rheumatic fever. So it is the issue of the streptococcal infection itself, not simply the issue, as I see it, of toxic shock or necrotizing fasciitis that should concern us.

As has been pointed out, the incidence, accurate incidence figures—and I would certainly agree with my two colleagues who just testified before you, accurate incidence figures are very difficult to come by—but I think we have to say that this severe infection represents a relatively rare complication. I think a lot of this is the result of maybe an exaggerated response in some cases by some irresponsible members of the press. This certainly was the case, because we have seen this infection, as Dr. Stevens pointed out, for the last 10 years in this country.

Why did this happen? Well, we don't really know the reasons. And I think if there is one message I would like to leave with you, we don't fully understand why this has happened. We don't understand its epidemiology, nor do we understand the basic science that is involved.

We do know that infectious diseases are cyclic in their nature. And we see this with influenza and a number of other diseases. But the molecular basis we don't understand.

Therefore, Mr. Chairman, I would say one of the things we do need is more epidemiologic research and more basic research.

I would point out, with all respect to our colleagues at the CDC who provide an extraordinarily important service to this country, that the committee should be at least made aware of the fact that most streptococcal research, the majority of it, takes place in universities and other institutes throughout the country. So it is not only needed, added needed resources at the CDC, which I think are important, but I think the whole problem of research on streptococcal infection needs to be addressed with more resources. I think they are inadequate at the present time.

I think that we would like to—well, I will just stop right now by saying thank you once again for the opportunity to appear before you. I would be delighted to answer any questions that you have.

[The prepared statement of Dr. Kaplan follows:]

**TESTIMONY PREPARED FOR**
**The Human Resources and Intergovernmental Operations**
**Subcommittee**
**of the**
**Committee on Government Operations**
**United States House of Representatives**

**July 28, 1994**

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Congressman Towns, Committee Members, Ladies and Gentlemen: I would first like to thank you for the invitation and the opportunity to appear before this Subcommittee to discuss the important medical and public health issues pertaining to and resulting from the group A streptococcal infections and their complications which have been so highly publicized during the past several weeks.

I am Edward L. Kaplan. Currently I am a Professor in the Department of Pediatrics at the University of Minnesota Medical School in Minneapolis, and also hold an appointment of Professor in the Division of Epidemiology at the University of Minnesota School of Public Health in Minneapolis. Additionally, of relevance to my appearance here today, I serve as Head of the World Health Organization Collaborating Center for Reference and Research on Streptococci located in the Department of Pediatrics at the University of Minnesota Medical School, a position I have held for the past nine years. Relevant to my qualifications to appear, to give testimony, and to answer questions before this Subcommittee on this subject is the fact that I have worked in the field of streptococcal infections and research for the past twenty nine years. I have been interested in and have published scientific papers relating to the diagnosis, treatment and prevention of these infections and their complications, the epidemiology of the infections, the pathogenesis of the infections and their complications (such as rheumatic fever/rheumatic heart disease and severe infections such as the streptococcal toxic shock-like syndrome, and the public health implications of group A streptococcal infections). Finally, I have and continue to give clinical medical

care to these patients and their contacts. I should also add that my clinical, epidemiological and laboratory experience includes significant experience in dealing with these infections and their complications in countries around the world where I have served in the role of consultant to Ministries of Health and to the World Health Organization to address these problems and to assist in the implementation of effective public health control programs. Details of these qualifications and interests are available in the accompanying biographical material and curriculum vitae.

Mr. Chairman, the Subcommittee's interest in assessing the impact of the problem of "*Invasive Strep A: What do we need to know?*" and group A streptococcal infections in general is very timely. This is not only because of the recent publicity given to these severe infections in this country and abroad, but especially because in my opinion and in the opinion of other clinicians, public health authorities and laboratory scientists, group A streptococcal infections constitute another of the common infections which continue to have the potential for causing significant morbidity and mortality even at the close of the twentieth century.

In order to specifically address the questions originally posed in your letter of invitation, I believe it necessary and important to provide background information about these infections. Allow me to first outline this information for your information before more completely addressing your questions. The background material will provide some of the answers you have asked for

There are a number of different kinds of streptococcal bacteria. (Streptococci are not viruses.) Today I will limit my comments to those streptococci which are called beta hemolytic streptococci because of the reaction that they cause on specific blood agar cultures plates in the laboratory. Although we can differentiate these beta hemolytic streptococci into several groups (designated by the letters A, B, C, G, etc.) by specific serological laboratory reactions, today I will concentrate only on the group A organisms. These are the ones which are most frequently the cause of beta hemolytic streptococcal infections in humans. Among the group A streptococci, there are at least 80 different kinds known as serotypes (these are designated by numbers such as 1, 2, 3, 4, etc.). However, there are, as we and others have shown, numerous other as yet either uncharacterized or incompletely characterized group A serotypes.

The most common type of human clinical infections caused by group A streptococci are those of the upper respiratory tract and of the skin. Most frequently the former infections are referred to as streptococcal pharyngitis or pharyngotonsillitis, or "strep throat", and the latter are referred to as "impetigo". These are very frequent infections, especially among children. In fact, these have been referred to as an "occupational disease of school children" because they are so common. It is difficult to provide you with precise incidence data because of reasons that I will come to in a moment, However, one group of estimates that I have seen which was prepared for the pharmaceutical industry suggested that there were at least four million cases of group A streptococcal pharyngitis during the year 1992 in the United States alone. All of us can recall having had "strep

throat" on numerous occasions as a school child, and we recall our own children's similar experience. Available data suggest that the use of antibiotics has not reduced the incidence of these infections since antibiotics were added to our therapeutic armamentarium. However, not only do these infections frequently involve school children, but also they have a propensity to involve other "crowded" or high risk situations such as medical facilities and even in military posts where outbreaks of group A streptococcal infections and their sequelae occur from time to time.

Most group A streptococcal infections are not severe. True, they do commonly cause the sudden onset of severe sore throat with high fever and often times abdominal pain and headache. The are a cause of absenteeism from school and from the work place, but they are most frequently limited to the upper respiratory tract. Fortunately, the organism usually can be eradicated from the upper respiratory tract or from the skin by the appropriate use of antibiotics. Antibiotic resistance has <u>not</u> been a problem with the group A streptococcus, in contrast to many other bacteria that have been described.

However, it is not the uncomplicated group A streptococcal infections of the upper respiratory tract or of the skin which have caused major concerns to physicians and to public health authorities over the years. For approximately fifty years we have known that these infections, if left untreated or undiagnosed, may result in what are referred to as non-suppurative complications, and these are more serious and dangerous problems. Rheumatic fever and the accompanying damage to heart valves can occur after these infections, as can a kidney disease called glomerulonephritis (or what many of us heard our parents call terms like "Bright's Disease") . Studies at the end of the decade of the 1940s and during the early 1950s showed clearly that prompt diagnosis and antibiotic therapy of streptococcal sore throat essentially can prevent rheumatic fever. The prestigious Lasker Award in Medicine was awarded for this outstanding clinical and epidemiological research. These studies made a very significant impact on management of an important and yet common bacterial infection.

Due to comprehensive educational campaigns directed both at the medical profession and at the lay public by organizations such as the American Heart Association, a greater understanding and a more encompassing approach to these infections resulted. It was an important step that is quite relevant to what we are discussing here today.

During the decades of the 1960s and 1970s and during the early part of the decade of the 1980s it is quite interesting that the incidence rates of complications of group A streptococcal infections were significantly reduced here in the United States, as well as in the industrialized countries of the world. Incidence rates of rheumatic fever dropped, for example, almost twenty fold. Careful studies in a number of places around the country documented this. One comprehensive study was carried out in Baltimore. Many cities such as Boston, New York, Baltimore, and Chicago which had entire hospitals devoted to the care of patients with rheumatic fever closed these hospitals during the 1970s. State health departments which had maintained rheumatic fever registries for decades

discontinued them. This happened, for example, in my own state of Minnesota in 1982. This decrease has not been experienced in many of the developing countries of the world, countries which as you are aware, make up approximately two thirds of the world population. There these complications have remained very important with incidence rates as high as or even higher than they had been in the United States several decades ago. Some attributed this reduction in the complications of streptococcal infections in the United States to the availability of antibiotics and to increases in standards of living here as well as to the availability of medical care. But these explanations, while undoubtedly having some impact, do not satisfactorily explain this apparent decrease in these complications. Because we do not yet fully understand precisely how these group A streptococcal infections cause rheumatic fever and severe systemic infections despite more than four decades of clinical, epidemiological, basic and applied research, we have no way of complete understanding why the decrease occurred.

There are some important clues. For example, in Monroe County in upstate New York, a comprehensive throat culture program for school children during twenty years between the mid 1960s to the mid 1980s suggested that while the number of cases of uncomplicated streptococcal sore throat did not significantly decrease during the twenty year period of time, the number of cases of rheumatic fever and glomerulonephritis fell almost to a non detectable level. This finding suggested that it was not simply that the incidence of the complications decreased, it was almost as if the group A streptococcal bacteria which caused these infections did not have the capability to lead to complications.

This example is important for two reasons. One is that this type of information probably lead to unwarranted complacency in the medical and public health communities. The disease had disappeared and was no longer a problem to be reckoned with in the United States (even though this clearly was not the case in other parts of the world). Microbiologists did not know what the "virulence factor" was that seemed no longer to be present, and clinicians and public health authorities were not very concerned because they did not see the disease. Many primary care physicians who were recent graduates of medical schools had never actually seen a patient with rheumatic fever, for example. A second important reason is that the epidemiological evidence suggested that the number of uncomplicated infections had not appreciably changed and, yet, the number of complications resulting from group A infections had decreased.

With that information in mind, let me attempt to relate this to the current situation in which we find ourselves and the reason for this hearing. In the mid 1980s this situation with group A infections began to change. There is what I believe to be convincing epidemiological evidence that, in the mid 1980s, severe group A streptococcal infections and complications of these infections were increasing. For example, several reported outbreaks of rheumatic fever were described from several parts of the country. The largest was that reported from Utah where it has been determined that more than 274 cases occurred between 1985 and 1992. This compares with an average of about 3-6 cases per year during the late 1970s and early 1980s. There was published epidemiological evidence suggesting that there were increases noted in more than twenty states. Of

relevance has been the fact that these outbreaks did not occur in socially and economically disadvantaged populations, but among middle class suburban populations with ready access to medical care. This was not just in children, but there were at least two outbreaks of rheumatic fever described among military recruits.

Similarly, during the mid to late 1980s, other types of severe infections with group A streptococcal disease were reported. Among the first significant series was a report published in the *New England Journal of Medicine* in July 1989. Twenty cases of streptococcal toxic shock-like syndrome were described. The mortality in that report and in other published series from United States and abroad has been as high as 30%. So it is important to recognize that these severe infections did not begin to occur in 1994 as reported recently by the tabloid press in England. They have been occurring since the mid to late 1980s. The initial reports in the United States also sparked interest and, to some degree, exaggeration by the press. After the initial reports, public interest declined until 1990 when Mr. Jim Henson died of complications of a group A streptococcal infection and then there was another period of heightened press interest, some of it quite exaggerated. We believe that the severe infections continued to occur in this country, as is documented by numerous published reports in medical journals. The same was true elsewhere in the world, particularly in Europe.

These infections have the potential for being very rapidly progressive. While precise mechanisms of entry of the bacteria into the body are not entirely clear, the group a streptococcus may enter the blood stream either through a break in the skin or from via the upper respiratory tract. While there are no bacteria that I am aware of that accurately can be described as "flesh eating," these group A streptococci associated with the severe systemic infections may cause necrosis of tissue and failure of organ systems such as the kidneys, the liver and the lungs. The virulence may well be related to the production of certain bacterial toxins by the bacteria which then cause pathological changes in the vital organ systems of the body and may then lead to the considerable tissue damage.

In June of this year there were reports of "flesh eating" bacteria in the British tabloids and the American public was once again made aware of this problem. Now, it is important to recognize that all states do not require reporting of group A streptococcal infections. In fact, there is a suggestion that less than half of the 50 states require any kind of reporting of group A streptococcal infections; some of the state requirements are only used in very specialized situations such as food borne outbreaks or hospital nursery outbreaks. This makes accurate determination of incidence of this problem extremely difficult, if not impossible.

A significant proportion of what has been publicized since June of this year has been considered by those with expertise in the field to represent exaggerated reporting by some of the electronic and print media. This is not to say that these severe infections are not more common now than they were in the early 1980s and before. But, despite the fact that there are, as far as I am aware, no published reliable figures documenting the precise incidence in the United States, most

scientists, epidemiologists and clinicians believe that this form of systemic infection is a relatively rare manifestation of group A streptococci. I concur. At the present time there is no need for public panic; there is a definite need for more complete understanding of the epidemiology and pathogenesis of the disease.

I believe that these severe group A streptococcal infections are more common than they once were; but these severe infections are not new. Careful examination of the medical literature clearly reveals that this type of infection has been observed and reported in the past, but not the recent past. Additionally, there is evidence to suggest that this became more common in the late 1980s. From our own experience, we think it likely reached a peak in the years 1990-1992 and has been decreasing, although certainly remaining more common than before the 1980s. Unfortunately, neither surveillance nor anecdotal reports will allow us to do more than to extrapolate estimates to determine any idea of the number of cases now or in the future. I do believe that the numbers of cases that have been estimated in many recent press reports have been exaggerated and are not founded upon clear supporting data.

The same is likely to be true for rheumatic fever, another very important complication of group A streptococcal infections. I think one can arrive at the informed conclusion that rheumatic fever is more common in the United States now than it was ten years ago, even though we probably have seen the peak of the "resurgence" three years ago. This opinion is based on an estimate, but I can provide document able examples from reports made to our laboratory from several different geographic areas in the United States during the past year.

There are no infallible means of clinically recognizing severe group A streptococcal systemic infection. The process may start as a rather vague flu-like syndrome with muscle aches and pains and a low grade temperature before it begins to rapidly progress. It may begin as an infected small cut or abrasion. It may present in other even less specific ways. It can be quite difficult for physicians to clinically diagnose in its early stages. Therefore, it usually is even more of a problem for untrained non-medical individuals. Fortunately this severe form of group A streptococcal infection likely is quite rare! The best advice to be offered at this time to the lay public regarding protection is that one should use common sense, and if there is an infection or if there are constitutional symptoms that normally would be of concern, the affected individual should seek medical care from his or her medical care giver. Reports in the press have suggested some guidelines for assisting the public in this difficult task. I would caution that none of these guidelines are so specific as to be absolutely diagnostic. Therefore, common sense remains the best approach to be used by the lay public.

Finally, in completing the background information and before addressing the issues related to what measures might be taken to address these infections, let me attempt to briefly address the enigma of why has this occurred. I believe that there is evidence to suggest that we have seen the introduction of more virulent strains of group A streptococci into some of the general population. We do not know yet exactly why these organisms are more virulent, in the same manner that we do not know exactly why we have seen a "resurgence" of acute rheumatic

fever during the past seven years. There are some important clues that have come from recent epidemiological and laboratory research in this country and from abroad. But this introduction and/or spread of strains with increased virulence should not be surprising. Examination of the history of infectious diseases and also of group A streptococcal infections in particular reveals a cyclic nature in the occurrence of infectious diseases. Historians recall the epidemics of plague and of small pox occurring in European cities during the middle ages. Recorded data reveal the cyclic nature of outbreaks of severe scarlet fever in Brighton, England at the end of the 19th century. (Scarlet fever is somewhat related to the type of severe streptococcal infections being considered in these hearings.) Public health authorities know the cyclic nature of influenza; there was a massive world wide pandemic in 1918 that is reported to have caused more than twenty million deaths. There have been epidemics in the late 1950s, in the late 1960s and from time to time since then. The cyclic nature of most infectious diseases is not only recognized for humans, but also for the animal kingdom. Outbreaks of rabies in bats and other animals on the East Coast have occurred recently, and we are aware of periodic outbreaks of tularemia (rabbit fever) and plague in prairie dogs in the west.

Therefore, the fact that we are seeing the introduction of some relatively few virulent strains of group A streptococci at the present time should not be unexpected. What we still do not fully understand is <u>why</u> this is happening. What are the changes among the group A streptococcal organisms that lead to its enhanced virulence? What causes the changes and what predisposes to the changes? What can physicians and the public health community do to more accurately predict these changes and their consequences? From a practical point of view, what can be done to more effectively treat the unfortunate few who contract this relatively rare infection, an infection with a recorded mortality rate of as high as 30% even with the best of medical care?

The Centers for Disease Control has been asked to assist in the understanding of this disease process and, as stated, the CDC has attempted to increase surveillance of these infections. However, recall that group A streptococcal infections are very common infections and one needs to understand more about the uncomplicated infections before fully understanding the epidemiology and pathogenesis of the complicated ones. It can be difficult to accurately assess the change in incidence of such a disease. This is for the reasons noted previously. To accurately predict the infections may be impossible, but it would require much more comprehensive surveillance if this were deemed advisable. On the other hand, I think that physicians are becoming more aware of these serious group A streptococcal infections. There has been a considerable amount of descriptive clinical material written in the recent medical literature about the disease.

Of interest to this Subcommittee should be the fact that many physicians are almost being inundated by the public inquiring because of what, at least in my opinion, are unnecessarily alarming reports. For example, as a result of this I find that pediatricians are being asked if mosquito bites cause the disease.

If I may, I would like to suggest that this infection, part of a spectrum of group A streptococcal infections of various kinds and of varied severity, still remains an enigma to clinicians and to biomedical scientists. There are many important basic questions that remain unanswered. I would respectfully submit that this group A streptococcal infection or syndrome is a classic example of yet another very common infection that has the potential for causing significant morbidity, mortality and expense but receives less than optimal appreciation of its potential for causing disease until either a famous person contracts it or the press publicizes it (perhaps sometimes to an extreme, as has been the case in a number of the reports published or broadcast during the past month or six weeks). From my comments it is possible to appreciate without difficulty the number of important gaps in our basic knowledge about the group A streptococcus and its infections and complications. When there were more than 20,000 cases of acute rheumatic fever reported in the U.S. Navy alone during the Second World War, it is not difficult to appreciate a response to needed research. These infections both here and also elsewhere in the world have shown us that they still constitute a significant threat. We need to learn more about how to control such threats. While it clearly is not the point of this hearing to examine the need for research funds for the medical and public health communities, one cannot discuss the pertinent aspects of these group A streptococcal infections without uncovering the existing gaps in our knowledge and concluding that these will need to be closed before this type of infection and its consequences can be prevented.

I want to emphasize that this need for more information and better control methods is not only one needed for the Centers for Disease Control and for the Public Health Service, but I think it appropriate to state that a very significant proportion - perhaps even the majority - of group A streptococcal-related research (including basic research into the mechanisms of disease, epidemiological research of group A streptococcal infections, and applied clinical research into diagnosis and treatment of these infections) takes place in laboratories and clinics at Universities and Institutes around this country and, indeed, around the world. Needs for these productive research laboratories and other facilities are not fully being met at the present time. Thus, while there is definitely a need for more attention to this matter at the Centers for Disease Control and within the Public Health Service, to adequately address the issue will require attention and resources made available to other facilities where expertise and experience are located.

Once again, Mr. Chairman and Members of the Subcommittee, I would like to thank you for the opportunity to appear before you today and to address this important issue. I will be glad to attempt to answer your questions or to respond to your observations.

7/28/94

Mr. TOWNS. Thank you very much, Dr. Kaplan.
Dr. Morse, you may proceed.

**STATEMENT OF DALE L. MORSE, M.D., M.S., DIRECTOR, DIVISION OF EPIDEMIOLOGY AND COMMUNICABLE DISEASES, NEW YORK STATE DEPARTMENT OF HEALTH**

Dr. MORSE. Thank you, Mr. Chairman.

My name is Dale Morse and I am director of the division of epidemiology and the State epidemiologist for the New York State Department of Health. On behalf of the department, I would like to thank you for the opportunity to testify today and share our thoughts and concerns.

Today I will be discussing invasive group A strep in New York State. But first I would like to address it in a broader context because it represents merely one symptom of the larger problem of emerging infections.

This emphasis is crucial because invasive GAS is but one of multiple important emerging infectious diseases which are being recognized as new, reemergent, drug resistant, nosocomially transmitted and/or epidemic in nature. This is essential because while today's scare terminology of flesh-eating bacteria has aroused the public, the press, and the scientific community's interest, the term could easily be applied to other tissue-invading organisms, such as Methicillin-Resistant Staph Aureus, or expanded to other organisms with such tabloid selling phrases as "mind eating" [meningococcus, rabies, et cetera] "lung eating" [hantavirus, et cetera] "blood eating" [HIV, malaria, ehrlichia], "gut eating" [for example, vancomycin resistant enterococcus E. coli 0157:H7, cryptosporidium], et cetera.

The major point for consideration is that they all require similar public health approaches and should be addressed on a comprehensive, rather than an individual basis.

As we have heard from the previous speakers, invasive group A strep is a severe manifestation of an infection with an organism which is found very commonly in normal, well individuals; occurs frequently as strep throat and impetigo, and is seen less frequently in association with scarlet fever, glomerulonephritis, toxic shock-like syndrome, and rheumatic fever.

Invasive GAS is rare, with an estimated 10,000–15,000 cases annually in the United States, which would extrapolate to approximately 700 to 1,000 cases a year in New York. To be honest, we don't know the exact number because it is not notifiable nationally, nor is it legally required to be reported in New York.

Historically, in New York, group A strep infections occurring on dairy farms were made reportable in the early 1900's because of raw milk associated outbreaks, but this became a nonissue with pasteurization and therefore was officially removed in 1986.

While not reportable, during the last decade we have responded to numerous press and public inquiries, especially after Jim Henson's untimely death due to such an infection in 1990 in New York City. We have distributed informational materials to hospitals and local health units on how to deal with the problem and information fact sheets, which is an attachment.

We have also investigated several group-based strep infections in schools, camps, and nursing home outbreaks. Another example is attached as a reference. And periodically we have reviewed hospital discharges of related conditions such as rheumatic fever to look for any potential increases, and also reviewed laboratory reports to look for any unusual clustering.

As an example, from September 1992 through January 1994, we worked with the State laboratory to solicit reports from 395 licensed bacteriology labs on an all-sterile site, that is blood and CSF, isolates of invasive group A strep of residents of New York State outside of New York City. While incomplete, that review of reported cases showed no differences by age or sex.

Cases occurred throughout the year with a peak in the winter, which you would expect from a seasonal perspective. Isolates were scattered among 14 counties and represented 20 different M and T types, and there was no evidence of time-space clusters. While somewhat reassuring, this type of passive surveillance is far from ideal, as it captured information on only about 10 to 15 percent of the estimated number of invasive group A illnesses.

New York has approximately 50 communicable diseases which are legally reportable by physicians, laboratories and health care institutions. Diseases are added to the list based on frequency, severity, transmissibility and preventability, such as vaccine or contact investigation for treatment.

In addition, outbreaks are legally reported and investigated. Despite its severity, invasive group A strep has not been made reportable because it doesn't meet the other criteria.

Furthermore, active surveillance for invasive group A strep alone would be time consuming and costly. Instead, it would be more cost effective to include invasive group A strep surveillance as part of a larger effort to conduct surveillance and control of a host of emerging pathogens.

Unfortunately, there are few if any resources to deal with a number of the currently notifiable conditions, let alone the nonreportable emerging ones such as invasive group A strep.

As an example, there are no Federal funds to support State and local reporting to the nationally notifiable disease system. And 95 percent of CDC Federal infectious disease funds are limited to surveillance in four categories, TB, HIV/AIDS, STDs and immunizable diseases. In New York, a similarly small percentage of funds is devoted to such agents, and New York's efforts exceed those of most other States in this regard.

In summary, inadequate resources are being devoted to invasive group A strep for research, for potential vaccine development, and other items which have been mentioned. But it only represents one leak in the dike. Rather than giving token funds to support fingers to plug this one hole alone, it would be more effective for Congress to help plug and control all emerging infection leaks by rebuilding the dike's infrastructure which has been neglected and eroded over the past two decades. Providing $150 million to fund CDC's emerging infection initiatives and increasing public health care support dollars to States would be an important step in the right direction.

Thank you. I would be happy to answer any questions.

[The prepared statement of Dr. Morse follows:]

NEW YORK STATE DEPARTMENT OF HEALTH

DIVISION OF EPIDEMIOLOGY

Testimony Before The

Subcommittee on Human Resources and Intergovernmental Relations

Congressional Committee on Government Operations

ON

# "INVASIVE GROUP A STREP"

Presented By

Dale L. Morse, MD, MS

July 28, 1994

--- CONGRESSIONAL TESTIMONY ---

Good morning, my name is Dr. Dale Morse and I am Director, Division of Epidemiology, and the State Epidemiologist for the New York State Department of Health. On behalf of the Department, I would like to thank you for the opportunity to testify today and share our thoughts and concerns.

Today I will be discussing invasive Group A strep (GAS) in New York State, but first I would like to address it in a broader context because it represents merely one symptom of the larger problem of emerging infections. This emphasis is crucial because invasive GAS is but one of multiple important emerging infectious diseases which are being recognized as new, re-emergent, drug-resistant, nosocomially transmitted and/or epidemic in nature. This more global perspective is essential, I repeat essential, because while today's scare terminology of "flesh eating bacteria" has aroused the public, press and scientific community's interest, the term could easily be applied to other tissue invading organisms (e.g., Methicillin Resistant Staph Aureus), or expanded to other organisms with such tabloid selling phrases as "mind eating" (e.g., meningococcus, rabies, herpes simplex), "lung eating" (e.g., hanta virus, drug-resistant pneumococcus, multiple drug-resistant TB), "blood eating" (e.g., HIV, malaria, ehrlichia), "gut eating" (e.g., vancomycin-resistant enterococcus, E. coli 0157:H7, cryptosporidium), etc. The major point for consideration is that they all require similar public health approaches and should be addressed on a comprehensive rather than an individual basis.

As we have heard from the previous speakers, invasive Group A strep is a severe manifestation of an infection with an organism which is found very commonly in normal well individuals; occurs frequently as strep throat; and is seen less frequently in association with scarlet fever, glomerulonephritis, toxic shock-like syndrome, and rheumatic fever. Invasive GAS is rare, with an estimated 10,000-15,000 cases annually in the United States, which would extrapolate to approximately 700-1,000 cases a year in New York. To be honest, we don't know the exact number because it is not notifiable nationally, nor is it legally required to be reported in New York.

Historically, GAS infections occurring on dairy farms were made reportable in New York in the early 1900's because of raw milk associated outbreaks, but this became a non-issue with the advent of pasteurization and was therefore officially removed as a reportable condition in 1986. While not reportable, during the last decade we have responded to numerous press and public inquiries (especially after Jim Henson's untimely death due to such an infection in 1990, in New York City); distributed informational materials to hospitals and local health units (Attachment 1); investigated several GAS school, camp and nursing home outbreaks (Attachment 2); and, periodically reviewed hospital

discharges of related conditions such as rheumatic fever and laboratory reports to look for an increased incidence or unusual clustering. As an example, from September 1992-January 1994 we worked with the State laboratory to solicit reports from 395 licensed bacteriology labs on all sterile site (blood, CSF) isolates of invasive GAS among residents of New York State outside of New York City. While incomplete, a review of the 86 reported cases showed no differences by age or sex (Attachment 3). Cases occurred throughout the year and more frequently during winter (as expected). Isolates were scattered over 14 counties, represented 20 different M and T types, and there was no evidence of clusters or outbreaks. While somewhat reassuring, this type of "passive" surveillance is far from ideal, as it captured information on only about 10-15 percent of the estimated number of invasive GAS illnesses.

New York has approximately 50 communicable diseases which are legally reportable by physicians, laboratories and health care institutions. Diseases are added to the list based on frequency, severity, transmissibility and preventability. In addition, outbreaks are legally reportable and investigated. Despite its severity, invasive GAS has not been made reportable because it doesn't meet the other criteria. Furthermore, "active surveillance" for "invasive GAS" alone would be time-consuming and costly. Instead, it would be more cost effective to include invasive GAS surveillance as part of a larger effort to conduct surveillance and control of a host of emerging pathogens. Unfortunately, there are few, if any, resources to deal with a number of the currently notifiable conditions, let alone the non-reportable emerging ones, such as invasive GAS. As an example, there are no federal funds to support State and local reporting to the nationally notifiable disease system, and 95 percent of CDC federal infectious disease funds are limited to surveillance in four categories (TB, HIV/AIDS, STD's and immunizable diseases). In New York, a similarly small percentage of funds is devoted to such agents, and New York's efforts exceed those of most other states in this regard.

Additional Comments: Establishment of "active" surveillance for invasive GAS would be difficult and expensive because, while invasive GAS is rare, GAS infections are extremely common. Requiring reports of all GAS would be impossible because of the sheer volume. Limiting reporting to only blood and CSF isolate infections would miss some cases, but be more manageable. However, it would still require regular contact with the 395 labs which might identify such isolates in New York State. Furthermore, since laboratory reports provide only limited information, meaningful surveillance would require intensive follow-up of individual cases to obtain demographic, clinical and epidemiologic data. This would require field staff to collect information from laboratories, physicians, hospitals, patients and their families.

Since the same laboratories usually process specimens on other emerging infections, it would be more efficacious to establish a more comprehensive system which would electronically transmit selected disease reports to state health departments and on to CDC for national surveillance, and to local health units for expedited follow-up. The need for establishing such an "emerging infection warning surveillance system" appears obvious, but would require more than "token" resources.

In summary, inadequate resources are being devoted to invasive GAS, but it only represents one leak in the dike. Rather than giving token funds to support fingers to plug this one hole, it would be more effective for Congress to help plug and control all the emerging infection leaks by rebuilding the dike's infrastructure, which has been neglected and eroded over the past two decades. Providing $150 million to fund CDC's emerging infection initiatives and increasing public health core support dollars to states would be important steps in the right direction.

Thank you. I would be happy to answer any questions.

Attachment 1 -- GAS Informational Material for Hospital and Local Health Units
Attachment 2 -- Sample New York State Department of Health GAS Manuscript
Attachment 3 -- Invasive GAS Lab Survey

Attachment 1

From: MAILER --ALBNYDH2 Date and time 06/24/94 12:40:03
Fri, 24 Jun 94 12:40:03 EDT
Received: by doh1f.hcom.gov (4.1/SMI-4.0-DNI)
id AA27485; Fri, 24 Jun 94 12:28:23 EDT
Date: Fri, 24 Jun 94 12:28:23 EDT
From: cpc01@albnydh2
Message-Id: <9406241628.AA27485@doh1f.hcom.gov>
To: cpc01@albnydh2

Subject: Perspective on Group A Streptococcal Infections

Attention To: Hospital Chief Executive Officer

E-Mail Message for Hospitals and Local Health Departments:

"Please distribute to appropriate medical,
infection control and laboratory staff"

Bureau of Communicable Disease Control
New York State Department of Health

June 27, 1994

PERSPECTIVE ON GROUP A STREPTOCOCCAL INFECTIONS

A. Morbidity/Mortality Trends

B. Clinical Spectrum

C. Public Health Aspects

D. Questions and Answers in GAS

E. References

Several recent news media reports describing cases of necrotizing fasciitis due to Group A Streptococcal (GAS) infections have lacked a scientific perspective on the disease and have failed to describe the overall context in which these cases have occurred. This informational report is intended to provide comments on trends of GAS, describe the spectrum of disease and highlight some of the public health issues.

## A. Morbidity/Mortality Trends

The absence of national or statewide surveillance data on GAS makes it difficult to identify changes in the epidemiology of GAS disease. However, a number of published laboratory based studies conducted in certain geographic areas have identified increases in invasive GAS infections in Arizona between 1985 and 1990 (1), Colorado between 1980 and 1990 (2) and Ontario between 1987 and 1991 (3).

Although complete surveillance data for invasive GAS in New York State is not available, a limited survey (unpublished data) of GAS isolated from sterile sites in upstate hospital labs between 9/92-1/94 identified 86 cases. No distinct time/space clusters were found, all age groups were affected, male to female ratio was 1:1 and 20 different M/T types (strains) were identified. More cases occurred between September 1993 and

January 1994 than for the same period September 1992-January 1993. Case outcome or frequency of necrotizing fasciitis was not available. The short duration of the study did not allow for trend analysis. Data must be collected in a consistent manner for multiple years in order to detect any significant changes in the incidence.

## B. Clinical Spectrum

In 1993 the CDC Working Group on Strep infections proposed the following classification of GAS (4).

| Class | Clinical Expressions |
|---|---|
| I | Streptococcal Toxic Shock |
| II | Other invasive infections defined by isolation from a sterile site including bacteremia or meningitis (with no identified focus); and cellulitis, wound infections, necrotizing fasciitis puerpural sepsis, septic arthritis (with an identified focus) |
| III | Scarlet Fever |
| IV | Non-invasive infections such as strep throat or impetigo |
| V | Non-suppurative sequelae such as acute rheumatic fever or glomerulonephritis. |

The clinical ~~factors~~ expression is mediated by a combination of host immune factors and virulence factors of the organism. The classification scheme reflects the broad clinical spectrum associated with GAS. The most common expression is streptococcal pharyngitis. Streptococcal toxic shock, septicemia and other invasive forms occur infrequently. Based on CDC estimates of 10,000-15,000 cases of invasive GAS per year in the United States, New York State would be expected to have 700 to 1050 per year.

## C. Public Health Aspects

In the absence of an effective vaccine, the public health focus is to encourage prompt diagnosis and treatment of streptococcal infection and educate the public regarding the epidemiology of GAS. The widespread publicity regarding necrotizing faciitis, although sensationalized by some of the media, may encourage patients to seek medical attention early in the course of their infection and minimize the risk of serious sequelae.

Although sporadic GAS is not presently a reportable disease, outbreaks occurring in schools, colleges, camps, health care facilities and state institutions must be reported to the local/state health department. Toxic Shock Syndrome (TSS), a Class I disease has been a reportable disease since 1986. However we are also interested in collecting surveillance data on other invasive forms (Class II).

In order to obtain additional data on sporadic cases, the BCDC requests that:

1. hospitals report cases of invasive GAS on a voluntary basis (defined as a patient with GAS isolated from a sterile site) to the local health department using the standard DOH 389 Confidential Case Report Form. A supplemental data form available from the NYSDOH has recently been developed to collect additional epidemiologic information.

2. laboratories continue to submit GAS cultures obtained from sterile sites and from patients with necrotizing faciitis to the NYSDOH Laboratory for M/T Typing.

A question and answer sheet intended for a general audience is attached. Questions regarding laboratory aspects can be directed to Clinical Microbiology Unit-NYSDOH-WCL&R at (518) 474-4177. To report cases, contact your local health department. For questions regarding the general epidemiology of GAS, call your local health department or the NYSDOH or NYCHD.

| | | |
|---|---|---|
| Greg Balzano | Buffalo/Rochester | (716) 847-4519 |
| Peter Drabkin | Albany | (518) 473-4439 |
| Rich Gallo/Helaine Leib | New Rochelle/Long Island | (914) 632-4133 |
| Marty Toly | Syracuse | (315) 426-7620 |
| John Marr MD (NYSDOH) | NYC | (212) 613-2440 |
| or | | |
| Marcy Layton MD (NYCHD) | NYC | (212) 788-4193 |

Additional information available from the Bureau of Communicable Disease Control, New York State Department of Health at (518) 473-4439 includes:

1. An example of a "Dear Doctor" letter on GAS developed by the Westchester County Health Department for those local health departments or hospital administrators who wish to communicate further with the medical community on this area.

2. Supplemental Case Report Form for GAS.

D. Question and Answer Sheet Adapted from U.S. Centers for Disease Control on Group A Streptococcal Necrotizing Fasciitis

May 26, 1994

Q. What is it?

A. Necrotizing fasciitis is a condition where muscle and fat tissue are broken down as a consequence of infection. Necrotizing faciitis is one manifestation of severe group A streptococcal infections. Other severe signs of illness that often occur with fasciitis are shock and organ failure (for example, kidney failure). Death may occur in 20-30% of patients with

necrotizing fasciitis. Other patients will require surgery, possibly including amputation.

Q. How common is it?

A. Studies conducted in the late 1980's indicated that severe group A streptococcal infections were becoming more common. Based on surveillance data from 1990, we estimate that 10-15,000 severe infections occur in the U.S. each year, resulting in 2-3,000 deaths. Intensive surveillance in the U.S. for severe group A streptococcal infections has not been conducted since 1991.

Of all persons with severe group A streptococcal infections, necrotizing fasciitis occurs in 5-10%. Persons of all ages may be infected although most disease occurs in adults. Often infection begins at the site of a break in the skin (a surgical or nonsurgical wound).

Q. Why does it occur?

A. Both the organism and host susceptibility likely play a role in necrotizing fasciitis. While most group A streptococcal cause only mild infections (such as "strep throat") some types may cause more severe disease. One factor that may be linked to necrotizing fasciitis is the production by some group A streptococci of proteases, enzymes that break down proteins. Host susceptibility also is important. Investigation of family clusters shows that the same type of bacteria can cause severe infection in one family member and mild or asymptomatic disease in others.

Q. How does necrotizing fasciitis kill?

A. Persons with necrotizing fasciitis are likely to develop spread and growth of the organism in many areas, including the bloodstream. When this growth continues unchecked it can lead to overwhelming bacterial infection and death.

Q. What can I do about it?

A. Necrotizing fasciitis often occurs in persons with wound due to surgery or injury which then become infected. Persons with such wounds should take appropriate measures to keep the wounds clean and should seek medical attention if signs of infection occur. The infection can be treated with readily available antibiotics.

Q. Can I safely travel to England where cases have been reported in the press?

A. Yes. Traveling to any area in England will not increase your risk of getting this disease. There are no travel restrictions for travel to any area in the U.K.Cases occur sporadically throughout the U.S., Canada and elsewhere.

Q. Is there a vaccine for this disease?

A. No.

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Attachment 2

718 INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY December 1992

## Readers' Forum

# Two Outbreaks of Primarily Noninvasive Group A Streptococcal Disease in the Same Nursing Home, New York, 1991

Louise-Ann McNutt, PhD; Aida E. Casiano-Colon, PhD; F. Bruce Coles, DO; Dale L. Morse, MD, MS; Marilyn Menegus, PhD; Annemarie Groth-Juncker, MD; Janet Lansky, MS; Karen Bell, MD; Benjamin Schwartz, MD

Group A *Streptococcus* has been identified as the cause of several outbreaks of infection in residents of nursing homes.[1-4] These reports described outbreaks that included persons with severe invasive disease as well as more limited infection. The purpose of this report is to describe an investigation of two consecutive outbreaks of group A *Streptococcus* that occurred in a single nursing home, where all affected residents had disease of mild to moderate disease severity. This report focuses on the identification of risk factors for infection and describes the approach used to control the spread of infection in the nursing home.

## BACKGROUND

In January 1991, medical staff at nursing home A recognized an increase in the occurrence of group A *Streptococcus* infections in residents of a 46-bed locked mental health unit, which primarily housed persons with dementia. This unit is located in the main building of a 471-bed, three-building facility. In May 1991, a second outbreak of group A *Streptococcus* affected residents of a skilled nursing care area on the floor directly above the mental health unit. Epidemiologic investigations were conducted to identify the extent of the outbreaks, modes of transmission, and potential risk factors for infection.

## METHODS

### Case Definition and Case Finding

A confirmed case resident was defined as any nursing home A resident with a positive group A *Streptococcus* culture between December 25, 1990, and July 4, 1991. A possible case resident was defined as any mental health unit resident with signs and symptoms consistent with group A *Streptococcus* infection, but for whom a culture was not obtained between December 25, 1990, and February 25, 1991.

We identified cases among mental health unit residents by reviewing medical records, reviewing the microbiology log, and culturing potentially infected sites from persons with group A *Streptococcus*-compatible illness. In addition, surveillance throat,

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*The authors thank Drs. John Elliott and Richard Facklam for laboratory support and Dr. Laura Fehrs for review of the manuscript.*

*Results from these investigations were presented in part at the American Public Health Association Meetings, Atlanta, Georgia, November 1991.*

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*McNutt LA, Casiano-Colon AE, Coles FB, et al. Two outbreaks of primarily noninvasive group A streptococcal disease in the same nursing home, New York, 1991.* Infect Control Hosp Epidemiol. 1992;13:748-751.

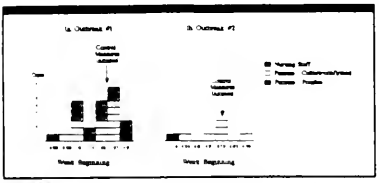

**FIGURE.** Group A streptococcal infection in residents and staff in nursing home A by date of symptom onset, New York, 1990-1991 Outbreak #1 (left) and outbreak #2 (right).

vaginal, and nasal cultures were collected from consenting residents. For visitors and staff members, only surveillance throat cultures were obtained. Case finding in other areas of the building were similar, but surveillance throat or nasal cultures were obtained only for close contacts of infected residents.

## ATTACK RATES AND RISK FACTOR INVESTIGATION

The existence of an outbreak(s) was determined by comparing group A *Streptococcus* attack rates in the affected areas to rates from other areas of the nursing home and from the previous year. To determine whether spatial clustering of case residents occurred, room locations were plotted.

We conducted a cohort study of risk factors of all residents of the mental health unit during the outbreak period. Potential risk factors, studied through a retrospective chart review, included demographics, behavioral factors, predisposing medical conditions, and the degree of nursing care, characterized by the amount of assistance needed with activities of daily living (e.g., feeding, toileting, bathing, and dressing). Categorical variables were analyzed by calculating relative risks (RR) and 95% confidence intervals ($CI_{95}$). Significance of association was determined using Fisher's exact test or chi square test as appropriate. A $p$ value of .05 or less was considered statistically significant.

### *Laboratory Methods*

Group A *Streptococcus* isolates were identified at a local hospital laboratory using standard methods (i.e., bacitracin susceptibility and streptex grouping). Available group A *Streptococcus* isolates were forwarded to the Centers for Disease Control for M-typing and T-typing.[5]

## RESULTS

### *Outbreak #1*

Of the 46 mental health unit residents, 13 (28%) met the confirmed and 11 (24%) met the possible case definition, respectively. Infection in the 24 case residents occurred between January 5, 1991, and February 2, 1991 (Figure). All available group A *Streptococcus* isolates were M-nontypeable, T-Imp 19. No group A *Streptococcus* infections had been documented in the mental health unit for at least 2 years prior to this outbreak. No group A *Streptococcus* organisms were isolated from residents living anywhere else in the nursing home during January and February 1991 (Fisher's exact test, $p<.001$).

TABLE 1
SITES OF GROUP A STREPTOCOCCAL INFECTIONS,* NURSING HOME A, NEW YORK, 1991

| Site | Outbreak #1 Culture-Confirmed | Outbreak #1 Possible | Outbreak #2 Culture-Confirmed |
|---|---|---|---|
| Wound/cellulitis | 5 | 5 | 4 |
| Eye | 3 | 5 | 1 |
| Ear | 2 | 0 | 1 |
| Nose | 2 | 1 | 1 |
| Sputum | 2 | 0 | 0 |
| Lymph node | 1 | 1 | 0 |
| Throat† | 1 | 0 | 0 |

* Five residents had two sites of infection
† Asymptomatic identified by surveillance culturing

Sites of infection in the cases were diverse. Ten residents had cutaneous infections (i.e., wounds, cellulitis) most often at sites without an apparent preexisting lesion; 8 residents had purulent conjunctivitis (Table 1). Two residents were hospitalized, and there were no deaths. All surveillance throat cultures from mental health staff (n = 37) and visitors (n = 15) and all vaginal cultures from residents (n = 38) were negative.

The risk of group A *Streptococcus* infection was significantly increased in residents needing total assistance with daily living (RR = 3.85, $CI_{95}$ = 1.06-14.29) and in residents with one or more chronic underlying conditions (e.g., diabetes, cancer) (RR = 2.44, $CI_{95}$ = 1.01-5.88) (Table 2). Analyses limited to confirmed case residents versus noncase residents (excluding possible case residents) yielded similar results. No clustering of cases by room location within the mental health unit was observed.

During the week prior to the outbreak, one nurse worked with symptomatic pharyngitis and reported having a positive throat culture for group A *Streptococcus* at her private physician's office. Although we could not epidemiologically confirm this nurse as the source of resident infections, several factors suggest that she may have introduced the group A *Streptococcus* into the facility and played a role in its transmission. These

TABLE 2
STUDY OF POTENTIAL RISK FACTOR EXPOSURES, MENTAL HEALTH UNIT, NURSING HOME A, NEW YORK, JANUARY 1, 1991—FEBRUARY 3, 1991; CONFIRMED AND POSSIBLE CASE RESIDENTS VERSUS NONCASE RESIDENTS

| Potential Risk Factors | Group A *Streptococcus** (n = 24) | Non-Group A *Streptococcus* (n = 22) | Relative Risk | Confidence Limits | p |
|---|---|---|---|---|---|
| Gender (female) | 19 | 19 | 1.25 | 0.67-2.33 | 0.702 |
| Race (Caucasian) | 23 | 20 | 1.60 | 0.32-8.14 | 0.467 |
| Median age (years) | 79 | 81 | NA† | | |
| Assistance with daily living | | | | | |
| Needs total assistance | 22 | 12 | 3.85 | 1.06-14.29 | 0.004 |
| No/moderate assistance | 2 | 10 | | | |
| Mobility | | | | | |
| Chairbound or >50% bed | 10 | 4 | 1.64 | 0.98-2.70 | 0.084 |
| No/little assistance | 14 | 18 | | | |
| Predisposing diseases | | | | | |
| One or more | 20 | 11 | 2.44 | 1.01-5.88 | 0.016 |
| None | 4 | 11 | | | |
| Medications‡ | | | | | |
| 1 or more | 18 | 11 | 1.75 | 0.87-3.57 | 0.079 |
| None | 6 | 11 | | | |
| Skin lesions | | | | | |
| Yes | 11 | 9 | 1.10 | 0.63-1.91 | 0.736 |
| No | 13 | 13 | | | |
| Visitors | | | | | |
| Yes | 7 | 5 | 1.17 | 0.65-2.09 | 0.619 |
| No | 17 | 17 | | | |
| Absences from unit | | | | | |
| Yes | 6 | 10 | 0.63 | 0.31-1.25 | 0.146 |
| No | 18 | 12 | | | |
| Mental status | | | | | |
| Confused/disoriented | 17 | 14 | 1.18 | 0.63-2.22 | 0.603 |
| Lethargy, apathy | 7 | 8 | | | |
| Incontinence | | | | | |
| ≥50% of the time | 17 | 11 | 1.56 | 0.81-3.03 | 0.148 |
| <50% of the time | 7 | 11 | | | |
| Nutrition | | | | | |
| Eats <75% of diet | 16 | 16 | 0.88 | 0.50-1.54 | 0.655 |
| Eats ≥75% of diet | 8 | 6 | | | |
| Oral fluids | | | | | |
| <75% recommended | 8 | 7 | 1.03 | 0.58-1.85 | 0.913 |
| ≥75% recommended | 16 | 15 | | | |
| Wandering behavior | | | | | |
| Yes | 10 | 8 | 1.25 | 0.32-4.86 | 0.713 |
| No | 14 | 14 | | | |

* Group A streptococcal disease (culture-confirmed [n = 13] and possible [n = 11])
† Not applicable
‡ Chemotherapy, steroids, analgesics, narcotics, hypnotics, psychoactive drugs

include a persistent sore throat while on therapy with subsequent group A *Streptococcus*-positive culture, more contact with case residents than noncase residents during the early outbreak period, and nursing assignments including only the affected unit, in contrast with most nursing staff who worked throughout the facility. In addition, the absence of symptoms and negative cultures from other staff members and visitors and the minimal movement of residents in and out of the nursing home suggest that this nurse was the most

likely source of the group A *Streptococcus* strain causing the mental health unit outbreak. Her isolates were unavailable for M-typing and T-typing.

### *Outbreak #2*

An additional 6 group A *Streptococcus* culture-confirmed case residents were identified in nursing home A between May 23, 1991, and July 4, 1991 (Figure). Prior to this cluster, one nurse had a positive group A *Streptococcus* culture (isolate not available). This outbreak included 5 (11%) of 46 residents on one floor and 1 (2%) of 46 residents two floors above (Figure). All resident isolates were M-nontypeable, T-3/13. Again, the most common site of infection was cutaneous (Table 1). The five residents on one floor all were clustered in one of three nursing areas (chi square = 11.59, $p = .003$).

### *Infection Control*

The nursing home implemented aggressive infection control measures. These included cohorting residents and staff, requiring masks and gloves with changes between resident contacts, and reinforcing handwashing behaviors. In the mental health unit, additional control measures included bathing residents with a germicidal soap and disinfection of all contact surfaces. No chemoprophylaxis to prevent secondary spread was given.

## CONCLUSIONS

These outbreaks highlight the potential role of ill employees in transmitting group A *Streptococcus* infection and the apparent effectiveness of infection control measures focused on barrier precautions in halting the spread of disease.

The employee health policy at nursing home A is typical of many others[6] in that if an employee is noted to be ill, they are required to take sick leave or, if that benefit is exhausted, leave without compensation. As a result, ill employees come to work and avoid precautions that could draw attention to themselves. The New York State Department of Health recommendations to nursing home A stated that symptomatic or culture-positive staff who could be a source for disease transmission must use barrier precautions or be removed from resident contact until a negative culture was obtained. In general, it is optimal for symptomatic personnel to be excluded from caring for high-risk residents, such as the elderly. Where this is not feasible, careful handwashing is essential, and the use of masks may be beneficial.[7]

Use of chemoprophylaxis appears to have been of benefit in aborting group A *Streptococcus* nursing home outbreaks that involved severe morbidity and mortality.[2,3] In contrast, in these two outbreaks of mild to moderate infection severity, no prophylaxis was necessary. Both outbreaks resolved quickly after improving infection control measures focusing on barrier precautions.

M-typing and T-typing were used to confirm links between cases within each outbreak and document that the two outbreaks were distinct. During the second outbreak, typing was used to guide infection control efforts. Without typing, aggressive and costly infection control measures, including chemoprophylaxis and cohorting of residents and staff, would have been implemented throughout the facility based on the assumption that the second cluster of cases represented an extension of the original outbreak and a failure of barrier control measures.

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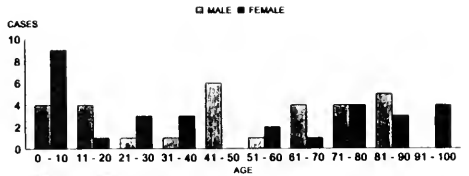
## Invasive Group A Strep Infections in NYS
## 9/92 - 1/94
## By Cases / Sex


■ MALE ■ FEMALE □ UNKNOWN

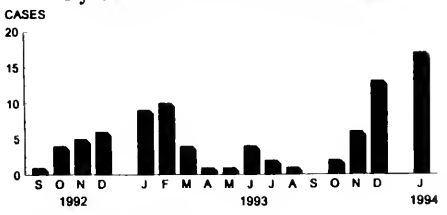
Typed and Non-Typed Cases Included
New York City Not Included In Sample

## Invasive Group A Strep Infections in NYS
## 9/92 - 1/94
## By Age / Sex




26 of 86 Cases Not Included - Sex and / or Age Unknown
Typed and Non-Typed Cases Included
New York City Not Included In Sample

## Invasive Group A Strep Infections in NYS
## 9/92 - 1/94
## By Cases / Month Received / Year




Typed and Non-Typed Cases Included
New York City Not Included In Sample

## Invasive Group A Strep Infections in NYS 9/92 - 1/94
## Type / County

| TYPE | COUN | TIES | |
|---|---|---|---|
| M-1 T-1 | ERIE | NASSAU | ONEIDA | ORLEANS |
| M-11 T-11 | CATTARAGUS | | | |
| M-12 T-12 | CHEMUNG | ROCKLAND | WESTCHESTER | |
| M-3 T-3 | NASSAU | | | |
| M-3 T-NT | ALBANY | | | |
| M-4 T-4 | ERIE | | | |
| M-5 T-5/27/44 | SUFFOLK | | | |
| M-51 T-14 | MONROE | NASSAU | | |
| M-6 T-6 | CHEMUNG | | | |
| M-NT T-11 | NASSAU | SCHUYLER | | |
| M-NT T-11/12 | ALBANY | CAYUGA | SCHUYLER | |
| M-NT T-13 | ALBANY | | | |
| M-NT T-14 | CHEMUNG | ERIE | SCHUYLER | |
| M-NT T-3 | ALBANY | | | |
| M-NT T-4 | ALBANY | MONROE | ONEIDA | |
| M-NT T-5/27/44 | NASSAU | | | |
| M-NT T-5/27/44/13 | ALBANY | | | |
| M-NT T-6 | ERIE | OTSEGO | | |
| M-NT T-6/14/MP19 | ALBANY | | | |
| M-NT T-NT | NASSAU | | | |

86 of 86 Invasive Cases Received Were Not Assigned Types  New York City Not Included In Sample

Mr. TOWNS. Let me thank both of you for your testimony.

Let me begin, Dr. Stevens, you remarked that many common public health approaches to infectious diseases do not work for strep A. Would you comment on that? I would like to hear you, Dr. Kaplan, on that.

Dr. KAPLAN. I am sorry, sir. I thought you said Dr. Stevens. I misunderstood that.

Mr. TOWNS. Dr. Stevens said that. It was Dr. Stevens' remark, if I remember correctly, that many common public health approaches to infectious diseases do not work for strep A. That was his comment. So I would like to get your opinion.

Dr. KAPLAN. Group A streptococci, as I pointed out, are very prevalent in the community. It is very widespread. If you go into any schoolroom in any community of the States or districts that you represent, in the middle of the winter, anywhere between 5 and 20 percent of the children in that schoolroom may have group A streptococci in their upper respiratory tract, in their throat. That doesn't mean they are ill at this point.

And perhaps he can correct me, if I were to try and interpret that, it is so widespread in the community that one cannot hope to wipe it out, so to speak, because there are many normal carriers of this organism. And therefore the common types of approaches to disease, epidemics and so on, really don't work when you have such a widespread organism.

If I can for just a second, I think if we don't understand the uncomplicated forms of an infection, if you will, it is very difficult for us then to understand the complicated form, the necrotizing fasciitis, the rheumatic fever. That is why it is so important that we do address the issue of this common infection.

Mr. TOWNS. Dr. Morse, would you have some comments on that?

Dr. MORSE. In terms of public health approaches, we unfortunately don't have a vaccine, for example, that we would use to try to control this infection. We don't do contact investigations to treat contacts, necessarily. But I believe I would point out that there are some public health approaches that could be applied to this condition that haven't been.

For example, traditionally in public health, you do surveillance, and not just passive surveillance but you try to establish active surveillance through laboratory based reports, through hospital and physician reporting of the severe infections. So more could be done in that regard in terms of looking at the problem, defining it.

Additional epidemiology studies could be done to identify individuals getting this infection combined with laboratory testing to determine if there are clusters or outbreaks where public health action would be taken, for example, an outbreak in a nursing home with an invasive group A strep.

We do cohorting and other infection control procedures to try to control it. Education is also a public health approach. It is important to educate both public and health care providers in order to recognize manifestations quickly.

Finally, based on knowledge gained from this surveillance, we consider targeted interventions with evaluation. And there are other diseases with past experience that we have developed ways of controlling through public health approaches.

Mr. TOWNS. Dr. Morse, your testimony suggests that strep A should not have a higher demand on our monitoring and reporting resources. Is that correct?

Dr. MORSE. I am sorry, repeat the question, please.

Mr. TOWNS. Your testimony suggests that strep A should not have a higher demand on our monitoring and reporting resources. Is that correct? Is that your position?

Dr. MORSE. Not exactly. I guess what I was trying to refer to is that I felt it should be put in context with setting up a system to conduct surveillance for all emerging infections. To set up a system for group A strep by itself could be fairly time consuming and require a lot of resources.

For example, there is some logistic difficulties in following up reporting. Group A strep itself is very common, and a number of hospital laboratories throughout the country could type for that. So if just group A strep infections were made reportable it would be a logistic nightmare in terms of the volume. There would just be too many cases to follow up on.

If we tried to focus on cases that were more severe or invasive and focused on central nervous system infections and blood cultures, that would be easier. And limited to fewer labs, but it wouldn't pick up all the cases that didn't have that kind of culture.

Logistically in New York State we would have to depend on 395 labs to report those types of infections. But that wouldn't provide us with enough information. We would need field staff working with local health departments to collect additional information from physicians on those cases.

So it would be a very time-consuming and costly effort to mount a surveillance activity by group A strep alone. But a lot of the same mechanisms could be used for other infections.

Mr. TOWNS. Dr. Kaplan, do you have any comments on that?

Dr. KAPLAN. Well, there is no question with the volume that I mentioned to you, that Dr. Morse is quite correct, to make it reportable in every instance would be an administrative and financial nightmare. I would certainly agree with that.

On the other hand, and perhaps my figures are not precisely up to date, but the last time I saw the figures that were reported, less than half of the States in the United States had a requirement for reporting streptococcal infections of any type, be they severe or common. And many of those that did require reporting had only very specific kinds of reporting required, for example, food-borne outbreaks or outbreaks in hospital nurseries. I think we probably could do a little better with that.

In other words, I think probably a realistic approach is somewhere in between the two. I think we could do better than we are now. Many States don't require reporting and therefore we don't have any idea of the problem until after the cat is out of the bag, as it were.

Mr. TOWNS. My time has expired.

Congressman Schiff.

Mr. SCHIFF. Thank you, Mr. Chairman.

Dr. Kaplan, Dr. Morse, I would like to ask you the same questions that I believe you heard me ask your colleagues. I want to preface it by saying that, again, on the one hand we know that

streptococcus infections have been around for a long, long time. And again, we also know, as Dr. Kaplan has observed, there has been very recently a great deal of reporting about streptococcus infection, particularly the so-called flesh-eating disease or necrotizing fasciitis, and oftentimes in a sensationalized kind of way.

So what I want to do is put this in perspective. What I want to know is, from your observations as medical doctors and professionals, either through an increased number of reported or known streptococcus A infections or through an increased number of severe forms of diseases that can be caused by group A streptococcus, even if the overall number is the same, or for any other factor, do we face a different situation today in terms of the threat to public health by streptococcus A infections than we did, say, 5 or 10 years ago?

Dr. Kaplan, may I call on you first, please.

Dr. KAPLAN. Yes, thank you, sir. My own personal opinion of this, and I think there are data to support this, is that there is no question in my mind that we are seeing more of these severe infections now than we did 10 years ago. I referred briefly in my remarks to the cyclic nature of infectious diseases.

The precise magnitude of that I think remains yet to be clearly defined at this point. Now, once that happens, and Dr. Stevens referred to this in his testimony also, we have had three ups and downs, if you will.

Initially when this was reported in the mid-1980's when Mr. Henson died and then more recently, as we see these increases in the amount of information that is given to the public through the press, then there are going to be more cases reported. And I think Dr. Broome reported the fact that this causes an artifact, too.

So the answer to your question specifically is, yes, I think there are more. My other answer is, we are not in the middle of an outbreak. It still remains, fortunately, rare. These complications remain rare. The more publicity we get, the more reporting we get, which gives us an uneven assessment of this.

Mr. SCHIFF. Is there any particular reason you would offer as to why the increased number of severe infections, complications is occurring now?

Dr. KAPLAN. I think, in my own opinion, it has to be related at least in large part to the appearance of organisms which are more virulent than they were 10 years ago. If you go back, for example, and look at streptococcal disease over a period of time, for example, if you look at Great Britain in the United Kingdom at the end of the last century, you see the same kind of cyclic phenomenon with scarlet fever, which is another manifestation of streptococcal infections.

I think it is clear from literature thus far that we are seeing organisms more likely to be virulent at this point, the emergence. If you ask me why that is the case, I can't answer it, and I am not sure anybody else can fully answer it at this point.

Mr. SCHIFF. But let me go back to the beginning of the hearing. I said I recommended this hearing to the chairman because the reporting, most recent reporting of these kinds of infections reminded me, at least personally, of the development of AIDS. It was reported as a very rare type of disease of an unusual nature but basi-

cally not as a public health threat. And of course we all know now, more than 10 years later, it is not the case.

So when you say you believe there is a more virulent strain of group A streptococcus, I am wondering if you mean something new that we can't control with penicillin, or is otherwise some kind of special threat.

Dr. KAPLAN. Your point is well taken. First of all, it should be stated categorically that resistance of group A streptococci to penicillin has not increased. That is in contrast to many other microbes that we have to deal with clinically. So I think that is not the situation.

What you are really asking me to do is to foretell what is going to happen 2 months or 2 years down the line. If I had to guesstimate, I would say this comparison with AIDS probably will not come to pass with the group A streptococcus. But I would emphasize that is a guess.

The basis for that is anecdotal. We don't have complete data that would allow us to make those projections, at least I am unaware of published complete data.

Mr. SCHIFF. Dr. Morse, you have obviously heard the questions. I would like your view. Essentially the question is, do we face a greater threat to public health in some way from group A streptococcal infections than we did five or 10 years ago?

Dr. MORSE. Briefly, from what the other speakers have presented and some reports in the literature, it appears there are some increases in certain types of invasive group A strep and certain strains which have more severe sequelae, as other people have mentioned.

In terms of New York State, we have not seen a marked increase, but I would point out that ours is a pretty passive reporting system. When we have looked at hospital discharge data for severe sequelae, for example, rheumatic fever, we haven't seen an increase in those type of cases.

And through our reporting network, like the laboratory reports that came in passively, we didn't see evidence of clusters or outbreaks occurring. However, that is an incomplete picture. We haven't heard reports of increased outbreaks from hospitals.

I think the press focusing attention on this kind of rare disease but one that has high mortality and affects normal individuals, though, points out the need to have a better active surveillance system to look at emerging pathogens such as this one. And people are no longer willing to accept the high mortality. For example, meningitis was a disease that now there is a vaccine for, and certainly invasive group A strep infections infect as many New Yorkers a year. So there does have to be more active surveillance to look at this and other infections.

Mr. SCHIFF. Mr. Chairman, before I yield back, I would like to make the observation that what I am hearing from all four witnesses is, when you set aside the sensationalized press about some of the more severe diseases that can be caused by streptococcus A, there appears to be a general agreement that there is an increase in the number of the severe forms of diseases that can be caused by streptococcus A, and it could well be this is a natural cyclical

result. It could be the result that the press reporting has brought out reports of the cases to the agencies that keep track of it.

On the other hand, the witnesses are also stating they are not quite certain. Certainly they are stating they are not certain where this is going to go. So I would suggest that when this hearing is concluded, we consider a report to the full committee that asks the Centers for Disease Control at the very least to monitor group A streptococcus infections more closely around the country and to advise the Congress of what they find.

I want to thank the witnesses, and I yield back.

Mr. TOWNS. Without objection, so ordered. Thank you very much.

At this time I yield to Congressman Payne.

Mr. PAYNE. Thank you very much.

I think that is an excellent recommendation, and I would like to associate myself with that.

I wonder, Dr. Morse, how are some diseases designated as being actively monitored? You mentioned a comprehensive approach is needed to curb a prevalent tide of infectious diseases.

For example, right now in New Jersey, we are experiencing another outbreak of E. coli infection. We had 35 cases reported recently throughout the State. And the very disturbing part of it is that it is very evenly divided throughout the State. It seems like it may not be just a single-source problem.

If the correct approach is not used, then we are not adequately prepared to deal with a potential epidemic. We saw, as I mentioned before, resurgence of tuberculosis.

Can you comment on an appropriate approach to dealing with strep A?

And second, as you have indicated, there is no reporting requirement for strep A. Either one of you may want to deal with this. How are you able to keep track of the disease? Is it just the fact that New York may have more initiative or Minnesota? And of course New Jersey. But if other States do not, how are we going to be able to monitor the disease's progression?

And also, of course, it was not a problem that occurred in New York. But the recent Legionnaire's disease that recurred on a cruise trip to New Yorkers is once again an example.

How are we going to follow up on this?

Dr. MORSE. I guess I would recommend approaching this similarly for group A strep with other of these rare emerging infections, and that is probably by improving the infrastructure to set up surveillance systems, to look at these infections, and to focus, for example, on laboratory-based reporting as a beginning point from laboratories that can report to State health departments with follow-up by local health unions to collect additional epidemiologic information.

One way of doing that is with laboratory based reporting to States, those reports could go on to CDC and also to local health departments. So part of this is using modern technology to improve the infrastructure that has eroded over the last several years in a number of States.

The potential of making it legally reportable obviously needs to be considered, and we are considering that. As I mentioned, there are logistic problems because group A strep infection by itself is so

common that it would not be logistically possible, so you would have to focus on maybe the most severe invasive forms, perhaps around bloodstream infections or central nervous system infections.

Again, though, to be effective, to make it reportable, there would have to be additional resources to really make it worthwhile. If we just get the laboratory reports with no additional information, that is not very meaningful.

So I guess the ways in terms of approaching it would be improving the infrastructure to have surveillance for this type of condition, focusing surveillance on certain States is certainly possible, as Dr. Broome mentioned, the five-State system, but that would have missed, for example, huntavirus or other conditions if you pick the wrong States.

So I think there is a need to improve surveillance for emerging infections on a larger basis. I think the State systems have the capability, but in recent years they have lost some of the capacity in terms of resources, and that has to be addressed now as we go into the era of health care reform as well because local health units may be losing additional resources as they are no longer providing primary care and some of the people that were involved with that were also doing public health followup as well.

Dr. KAPLAN. Congressman Payne, I would really address this in two ways. One relates to priorities, of course, and the other relates, as Dr. Morse just said, to resources. I think resources are important in two aspects. Keeping track of these, in my own State, in Minnesota, we had a very large rheumatic fever registry which we kept track of for many years. This was discontinued in 1982 simply because of lack of resources. And this is documentable in other States also.

So I think if there are resources that are available, a lot better job can be done. Just exactly how one wants to do it, of course, can be determined.

The second approach that I would take to answer your question would be, there are an awful lot of questions that are unknown that the four of us who have talked to you today have been unable to answer about this organism. We need more basic research. We need more epidemiologic research. We need more applied research in how do you diagnose and treat this. That, once again, comes back to funding. And that funding is on a little different level than at the State health department level.

It is in the form of research, not only in CDC, as I pointed out in my testimony, but I think elsewhere, where there is an incredible amount of expertise in this country. Streptococcal infections are a major problem around the world and this country has been a leader in that field for many years. We have an awful lot of expertise here. And it is funding that is going to help us successfully address this.

Mr. PAYNE. Thank you very much. I see my time has expired.

I think the points you bring out here are very important, priorities and resources, and the resources are allocated by the priorities. So I am not sure which comes first. It should be—and one disturbing thing in the past, I think there is a new spirit in CDC and NIH, but in the past, a decade ago, the priorities were not based necessarily on the severity of the problem. The priorities were

based on maybe politics. When the first AIDS's case was diagnosed in 1978, it wasn't until 1982 that the administration at that time decided to have a $200,000 allocation to study this thing called AIDS, because it afflicted people who were ne'er-do-wells, they were people who were doing the wrong thing, they were out of the mainstream, on the margin of society they were poor people, they were drug abusers, they were homosexual people. And so the priorities were not high. The priorities were very low. As a matter of fact, it remained low through the 1980's because these were people who were not important.

And so I know that this affects people, Native Americans, African Americans, alcoholics to some degree, people who have deficient immune systems, people who are intravenous drug users. And I am hoping, with the new CDC and NIH leadership, that we do not fall into the category again of this being a low priority, and therefore lower resources being applied to it.

And I also agree that in addition to the research being done on the CDC level, I understand about $11 billion is spent annually on research to the Federal Government, through universities. But about $12 billion is spent by private industry, pharmaceutical companies and the rest, where the applied research is done. So there would have to be the combination or coordination of the two.

But I am concerned that we don't—you know, when the Legionnaire's disease came out, there was a tremendous amount of resources put into that. If you remember, it was 15, 20 years ago. Why? They were veterans, they were practically all white men, they were good Americans who served their country, they were former, you know, high-level personnel, and as I mentioned, former veterans. And so there was a concern that the resources went into it, and they detected in a relatively short time a very difficult disease to detect.

As I indicated, the resources, when it came to AIDS, were not there because it was a totally different population.

And lastly, women have been left out. When they did the testing of aspirin on the effect of strokes, 22,000 men were used, and not a single woman. But stroke and heart disease afflict women at higher rates than men. So women were also put in this other category.

Thank you.

Mr. TOWNS. The gentleman's time has expired.

I now yield to Congressman Portman.

Mr. PORTMAN. Thank you, Mr. Chairman, and thank you for having the hearing. You and the ranking member have done a service I think to bring these witnesses before us and clarify many of the issues we have seen reported in the media. It certainly puts this flesh-eating bacteria in perspective.

I have had a number of questions that have already been addressed by the panelists. I do think I ought to give Dr. Kaplan a chance to respond to Mr. Payne's comments, because he seems eager to do that.

Dr. KAPLAN. Thank you.

I just wanted to agree with the Congressman, to point out that historically streptococcal infections have been associated with so-

cially and economically disadvantaged populations. And it is important to know that.

However, it is equally important, it seems to me, to note that in the recent outbreaks, especially those related to rheumatic fever, if one looks at the data, for example, from Salt Lake City, this has occurred in middle class populations, with ready access to medical care. So it is not quite so simple, at least in my opinion.

We think that the former is related to crowding, because infectious diseases obviously spread with crowding. But it really affects a very broad base of the population. And I think you are quite right that we have to look at all aspects.

Thank you for that opportunity.

Mr. PORTMAN. You are welcome.

I agree with Mr. Schiff, it would be good to have some follow up and to have a report go to the full committee on the issue of group A streptococcus generally and certainly the flesh-eating bacteria that has been in the press so much.

I guess my questions that remain, Dr. Morse and Dr. Kaplan, really go to the issue of how to increase the monitoring. You talked a lot about surveillance, Dr. Morse, the need for more infrastructure and funding for that.

One of the specific questions I have had is how to have more international reporting and information gathered. It seems to me that this particular issue is one we have seen raised in Europe, Australia, really around the world.

Is there a need for some sort of international clearinghouse? Can CDC play that role? Or do you all see the need for some other international body to play that role? I would like to hear from both of you on that.

Dr. KAPLAN. If you like, as mentioned, I do head a World Health Organization streptococcal reference laboratory. There is a network of these, and there is great interest around the world. Streptococcal infections are an incredibly large problem around the world. They are the major cause of cardiovascular disease, rheumatic fever, in developing countries, which make up two-thirds of the world's population.

The World Health Organization has taken note of this new resurgence, and in fact there will be meetings held, and there are ongoing meetings to discuss the approach.

Once again we come back to priorities and resources. When you see what is happening in Rwanda, for example, where do we put this in terms of priority?

So there is an international, ongoing effort to address these issues in the developing countries which have no resources, and where this is a very major problem, as well as what we have seen in Western Europe in the last few years, in Australia and New Zealand, and in Southeast Asia.

So the answer to your question is, basically there is. It always can be enhanced. Once again we come back to the same issues of priorities and resources.

Mr. PORTMAN. And it is your view that the World Health Organization would be the appropriate body?

Dr. KAPLAN. It would certainly be one of those, and it is. As a matter of fact, I can tell you that I just talked about this with them

within the last week, and there is great interest and there is effort that will be extended there, at least two WHO meetings that I know about that will take place within the next 6 months to take care of this.

Dr. MORSE. I would agree with Dr. Kaplan's comments. There is a need for international monitoring. WHO, CDC, are good places to start, plus the reference laboratories like Dr. Kaplan works with in terms of WHO.

The European Community has a network they are developing with the Public Health Laboratory Service in England. I guess one concern would be the developing countries. Most current surveillance is in the developed countries, and I don't think we should forget the developing ones. Working with WHO and CDC and other agencies that already have contacts would probably be useful.

I just want to address one other comment in terms of the monitoring. I know a lot of this depends on priorities and where resources will go to set this up. But I guess I would point out one thing that hasn't, I don't think, been discussed too much, are costs—whether the costs that are involved currently in terms of hospitalization and chronic sequelae—we shouldn't forget that those costs hopefully would be reduced by putting some priority and funding into preventive-type action. I didn't want to lose sight of that.

Mr. PORTMAN. Thank you.

Thank you, Mr. Chairman.

Mr. TOWNS. Thank you very much, Congressman Portman.

Let me just conclude by saying that I agree with you. I think that a piecemeal approach is not a solution to the problem. I don't think that we really can tackle the problem until we have enough information; and in order to get the information, we have to monitor. There is no other way.

I think you are right. We will find if we monitor and move aggressively, in the long run we might be able to save money, but one thing is certain: We definitely would be able to save lives, and I think that is very, very important.

As we talk about health care reform and talk about the Health Security Act, I think that infectious disease is something that should be talked about as well; the fact is that electronic reporting of some sort should be a part of this discussion. If we are really going to reform health care, in the sense that I look at reform—the more I hear about it around here I am not hearing reform, I am hearing retreat. So I am having a problem with that.

But I think if we are going to look at the monitoring that we have, the kind of electronic reporting system which could be put in place, that would not require a lot of energy or time on anybody's part because there will be uniformity of recordkeeping and things of that nature, that would be able to give us the information that we need to give you so that you would be able to really monitor this. Because I am hearing something here that I must admit that I am excited about the fact that you are saying that this situation is overblown and grossly exaggerated and it is not as bad as the media would say, but at the same time you are saying to us: We are really not sure what is going on because we don't have all the information, and we don't have the necessary resources to go and

to do the kind of things that need to be done, so therefore we are giving you our best at this time. We need to look further. I think that is an honest assessment. I think that conclusion is very important.

I must say that I am happy to know that, while strep infections are common among children, the gruesome invasive infections are not common, especially among children. That is encouraging. But at the same time when you don't have all the information, you wonder about those kinds of statements as well. When we say that we do not have the monitoring, that some States don't do anything, and that we hear about it basically through the media.

Let me just say I was back in my district some time ago, and they had done an interesting analysis wherein over the past week they found out that five people had cars that were stolen from one block. So they decided to do some research. They went and interviewed everybody that lived on the block, only to find out that 90 percent of the people that lived on that block had had their cars stolen over the last 10 years.

They thought it was something that happened over a week. But came to realize this had been going on for quite some time, but nobody had talked about it.

I am concerned that what we are dealing with here might be bigger than what we realize it is, but we have not been talking about it. I think the analogy used by Congressman Payne about AIDS definitely could be used here. I think we need to guard against it, we need to be careful, and I think that in order to do that we have to have as much material as possible.

So along with the report, Congressman Schiff, I would like to take that a step further. I think that we should meet with CDC; I think we should meet to try to see what can be done to get the resources to the proper places. I think that we are talking here about commitment. To me, this is very, very important.

So I would say to you that I will ask for such a meeting to see if we can talk about getting this coordination going, because here, again, this might be bigger than we realize it is.

I would like to thank the witnesses for coming and for testifying.

This hearing is now concluded.

[Whereupon, at 11:40 a.m., the subcommittee adjourned, to reconvene subject to the call of the Chair.]



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